ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 50, NO. 3



MARCH, 1959

Contents

| Effect of the Cardiae Arthythmias on the Coronary and Systemic Circulations. ELIOT CORDAY, HERELT GOLD, LAURO B. DE VERA, JOHN H. WILLIAMS and JOSHUA FIELDS | |
|---|--|
| | |
| Hyperventilation from Organic Disease. PHILIP R. ARONSON | |
| | |
| Problems in the Cortic Meroid Therapy of Rheumatic Disease. WILHUR BLECHMAN and JOHN H. VAUGHAN | |
| Clinical Evaluation of Remandialyliminourca, a New Riguanide Oral Blood Sugar Lowering Compound: Comparison with Other Hypoglycemic Agents, 1 to P. Krall and Robert F. Bradley | |
| The Problem of Staphylococcal Infections in Infants and Children, I HOMAS E. SHAFFER | |
| Laboratory Acquired Tularemia in Vaccinated Individuals: A Report of 62 Cases. THOMAS E. VAN METRE, Jr. and PAUL J. KABULL | |
| Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Twelfth Rheumatism Review). Part II. Charley J. Smyth, Joseph J. Buniat, Wichtig S. Clark, Darrell C. Crain, Felin E. Demsoting, Ivan F. Duff, Ephratu P. Engleman, Donald C. Crain, Max M. Monthomery, Bernard M. Norchoss, Howard F. Polley, Marian W. Ropts and Edward F. Rosemberg | |
| | |
| Serum Hypertopicity Secondary to Cerebral Disease, Marvin F. Levitt. Marvin Bellicy and Demetra Polimeros | |
| Tuberculoms of the Brain with Tuberculous Adenitis and Epidiuvnitis SHEL- | |
| | |
| | |
| | |
| Staphylococcal a pricemia with Recurrent Spontaneous Presunctions. Attended School College and Joseph Fights 1988 | |
| | |
| Reviews | |
| College News Notes | |

FORTIETH AMNORIE SESSION — CHICAGO, ILLINOIS, APRIL 20-24, 1959

In Asthma

The Most Important

Medihaler

after the property of a section of the section of t

Available

with either epincohrine

or isoproterenal

Medihaler-EPI

Kolnerman buntrur trans un sing same and inter-

Medihaler-ISO

J. Dopro A. dol suthing v.H. nig. carties from the first property of the property of the property of J. Dolland Science of the property of



Subscription per samum, het postpaid, \$1500, Hatted States, Canada, Hawali, and Puerto Kieo; \$11.0 riother countries.

ASCHHEIM-ZONDEK TEST • BALDY WEBSTER SUSPENSION • BANDL'S RING • BARTHOLIN • GLANDS BASSET OPERATION . BAUDELOCQUE'S DIAMETER . BRACHT MANEUVER . BRAXTON HICKS . CONT CONTRACTIONS . BRAXTON HICKS VERSION . BRENNER TUMOR . CALL-EXNER BODIES . CANAL OF

OBSTETRIC

TEIN-LEV

JRMDOR

CEPS TR

URNER'S

IOBOKEN

POSITION

WATKINS

A OPERT LLY . W

· ASCH

ALDY WE

NDL'S RI

BASSET

E'S DIAM

IVER . B

)NS . BR

BRENNER

S - CAN

K'S SIGN

· CLOQ

AIRE UTE

CREDE

N . CUR

IES BALL

3ACILLUS

UNCAN'S

BES . FR

N . FRIE

I'S DUCT

CLES . H

R'S SIGN

HODGE

· STRO

CUNIRAGITUMS • BRAXION HICKS VERSION • BRENNER TUMOR • CALL-EXNER BODIES • CANAL OF NUCK • CHADWICK'S SIGN • CHIARI-FROMMEL SYNDROME • CLOQUET'S NODE • COUVELAIRE • UTE UTERUS • CREDE MAUEUVER • CREDE PROCEDURE • CULLEN'S SIGN • CURVE OF CARUS • DE RI RIBES BALLOON • DODERLEIN'S BACILLUS • DUHRSSEN'S INCISIONS • DUNCAN'S MECHANISM • FA FALLOPIAN TUBES • FRANKENHAUSER'S GANGLION • FRIEDMAN TEST • GARTINER'S DÜCT • GIGLI SAW • GRAAFIAN FOLLICLES • HEGAR'S DILATORS • HEGAR'S SIGN • HILLIS-DELEE STETHOSCOPE HODGE PESSARY • HOFBAUER CELLS • HOLMES PACKER • HUHNER TEST • HYDATIDS OF MORGA MORGAGNI • IRVING STERILIZATION • KIELLAND FORCEPS • KRUKENBERG TUMOR • LANGHANS LAYER • LATZKO OPERATION • LE FORT OPERATION • LE'S GANGLION • LEOPOLD MANEUVERS LITZMANN'S ASYNCLITISM • MACKENRODT'S LIGAMENTS • MACKENRODT'S LIGAME MAURICEAU MANEUVER . MEIG'S SYNDROME . MICHAELIS' RHOMBOID MANCHESTER OPERATION . MONTOGOMERY'S TUBERCLES . NAEGELE'S ASYNCLITISM · NAEGELE'S RULE · NEISSERIA GONORRHOEAE · ORGAN OF ROSENMULLER PAPANICOLAOU SMEAR - PFANNENSTIEL INCISION - PFLUGER'S OVARIAN TUBULES - PIPER FORCEPS POMEROY STERILIZATION • PORRO OPERATION • POUCH OF DOUGLAS • RITGEN MANEUVER • ROB ROBERT PELVIS • RUBIN TEST • SCANZOMI MANEUVER • SCHILLER TEST • SCHUCHARDT INCISION SCHULTZE'S MECHANISM . SPECULUM . SKENE'S DUC SPACE OF RETZIUS . SPAI ASCHHEIM-ZONDEK TEST • **DENMAN - SPONTANEOUS E EVOLUTION OF DOUGLAS** • STEIN-LEVENTHAL SYNDRON STROGANOV REGIMEN . ST PROCEDURE . TARNIER FO TRENDELBURG POSITION . SYNDROME . VALVES OF **VOORHEES BAG • WALCHER** WALTHARD CELL ISLANDS . INTERPOSITION . WERTHE OPERATION - WHARTON'S JE WOLFFIAN BODY AND DUCT ASCHHEIM-ZONDEK TEST • B WEBSTER SUSPENSION . BA RING . BARTHOLIN GLANDS **OPERATION** • BAUDELOCQUI DIAMETER . BRACHT MANEL **BRAXTON HICKS CONTRACTIO** BRAXTON HICKS VERSION . TUMOR - CALL-EXNER BODIE CANAL OF NUCK . CHADWIC CHIARI-FROMMEL SYNDROME CLOQUETS NODE . COUVEL **UTERUS - CREDE MANEUVER** PROCEDURE - CULLEN'S SIG CURVE OF CARUS . DE RIE BALLOON . DODERLEIN'S I DUHRSSEN'S INCISIONS . D MECHANISM • FALLOPIAN TU FRANKENHAUSER'S GANGLIO FRIEDMAN TEST - GARTNEF GIGLI SAW . GRAAFIAN FOLLI HEGAR'S DILATORS . HEGA HILLIS-DELEE STETHOSCOPE ESSARY . HOFBAUER CELL

HOLMES PACKER . HUHNER TEST . HY

FORCEPS • KRUKENBERG TUMOR • LAN LEE'S GANGLION • LEOPOLD MANEUVER

Obstetric and **Gynecologic Milestones: Essays in Eponymy**

· SIMPSON FORCEPS · SIMS POSITION · SIMS

T . SMELLIE FORCEPS . SMELLIE SCISSORS . SP

LBERG'S CRITERIA . SPONTANEOUS EVOLUTION OF ENSION . BANDL'S RING . BARTHOLIN .

MULLERIAN DUCTS . NABOTHIAN CYSTS . NAEGELE PELVIS . NAE

HAROLD SPEERT, M.D.

Assistant Professor of Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons: Assistant Attending Obstetrician and Gynecologist, The Presbyterian Hospital, New York.

Dr. Speert tells the stories—some for the first time, others long forgotten-behind the eponymic nomenclature of obstetrics and gynecology. Each of the 79 chapters is an independent essay, including a description of related earlier work, and biographic sketches, liberally salted with portraits and original illustrations.

Dr. Speert allows the original authors to speak for themselves, through extensive quotations from their own writings, many of which are translated into English for the first time. Never before has all of this material been collected in one volume.

217 illustrations 700 pages December, 1958 \$15.00

> The Macmillan Company 60 FIFTH AVENUE NEW YORK 11, N.

CATION . KIELLAND E FORT OPERATION MADLENER STERILIZATION . MANCHESTER OPERATION . MAURICEAU MANEUVER . MEIG'S SYNDROME



The picture of health—no "angina problem" ...on Metamine Sustained, b.i.d.

When anginal episodes persist in spite of E.C.G. evidence of "good recovery" from myocardial infarction, METAMINE SUSTAINED provides ideal protective medication. In fact, METAMINE SUSTAINED protects many patients refractory to other cardiac nitrates, reducing the number and severity of anginal attacks, or eliminating them entirely. Dosage is easy to remember: "I tablet on arising, and I before the evening meal."

Each tablet of METAMINE SUSTAINED slowly releases 10 mg. of aminotrate phosphate (LEEMING), the long-acting coronary vasodilator

virtually free of nitrate side effects (nausea, headache, hypotension). And, when you prescribe METAMINE SUSTAINED your angina patient will need less nitroglycerin and thus remain fully responsive to that vital emergency medication.

Supplied: bottles of 50 and 500 sustained-release tablets. Also: Metamine (2 mg.); Metamine (2 mg.) with Butabarbital (1/4 gr.); Metamine (10 mg.) with Butabarbital (1/4 gr.) Sustained; Metamine (10 mg.) Sustained with Reservine (0.1 mg.).

Thes. Leeming & Co. Inc. New York 17.

Eisfelder, H.W.: Case history 4/35. Personal communication. 2. Fuller, H. L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy, 3:322, 1956.



HOEBER-HARPER

BASIC CLINICAL BOOKS

BAYLEY'S Biophysical Principles of Electrocardiography

New and fundamental! An eminent investigator and teacher explains and illustrates, in careful detail, the basic knowledge essential for understanding the electrocardiographic wave form. Required information from electricity and mathematics is reduced to easily-understood methods. This new book will supplement, not duplicate, texts now on your shelves.

By ROBERT H. BAYLEY, M.D., Prof. of Medicine, Univ. of Oklahoma. 255 pp., profusely illus. \$8.00

HOOBLER'S Hypertensive Disease

New! Here in one book is a complete summary of the details of diagnosis and management of all forms of elevated blood pressure, whether primary or secondary to other diseases. Contains 12 appendices designed to give precise working details of various tests and accepted treatment regimens.

By SIBLEY HOOBLER, M.D., Assoc. Prof. of Medicine, Univ. of Michigan, Director Hypertension Clinic, Univ. of Michigan Hospital. \$7.50.

NACLERIO'S Bronchopulmonary Diseases-2nd Printing

Foreword by Richard H. Overholt, M.D. 142 eminent authorities prepare a comprehensive clinical volume, covering the whole field of thoracic disorders—basic aspects, diagnosis, and treatment, from embryology to the newest therapy of every type.

By 142 Authors. Edited by EMIL A. NACLERIO, M.D., Chief of Thoracic Surgical Services, Harlem and Columbus Hospitals, N. Y. 983 pp., 719 ills. \$24.00

PALMER'S Clinical Gastroenterology

Bedside medicine. Diagnosis and therapy with recommendations based on personal experience and especially prepared clinical illustrations. By one of the country's most thoughtful and original gastroenterologists.

By Eddy D. Palmer, M.D., Lieut. Col. U.S.A.; formerly Chief of Gastroenterology, Walter Reed Hospital. 640 pp., profusely illus. \$18.50

| \$24.00 |
|----------|
| .\$18.50 |
| |
| |
| |

Please Mention this Journal when writing to Advertisers

JUST READY—NEW 10th (1959) EDITION

Joslin's Treatment of Diabetes Mellitus

By

ELLIOTT P. JOSLIN, M.D. HOWARD F. ROOT, M.D. PRISCILLA WHITE, M.D. ALEXANDER MARBLE, M.D.

New England Deaconess Hospital, Boston, Massachusetts

This classic work has long been proved to be one of the most useful books ever published on the understanding, diagnosis and treatment of diabetes mellitus. It is based on experience gained from treating more than 51,000 diabetics of all ages, including 1700 pregnant diabetics. Separate chapters are devoted to diabetes in relation to virtually every one of the specialties.

Every chapter and nearly every page has been revised and brought up to date. Oral use of the sulfonylureas is reported, with succinct rules for their use and summaries of treatment based on several thousand of the authors' cases. Stress throughout is on exercise, diet, insulin or oral medication, and on instruction to the patient, especially in the hospital teaching clinic.

New 10th (1959) Edition. About 800 Pages. Illustrated. Just Ready. Approx. Price \$15.00.

Washington Square LEA & FEBIGER

Philadelphia 6, Pa.



"...effective as a euphoriant...and as an energizing agent against weakness, fatigue, adynamia and akinesia... potent action against sialorrhea, diaphoresis, oculogyria, and blepharospasm...also lessens rigidity and tremor... minimal side reactions...safe...even in cases complicated by glaucoma.'

ay, L. J., and Constable, K.: J.A.M.A. 163:1352 (Apr. 13) 1957.

Riker

Northridge, Californi

Please Mention this Journal when writing to Advertisers

A LARGER SELECTION OF PULMONARY FUNCTION EQUIPMENT FROM

COLLINS

From the modest beginning in 1942 of only one piece of pulmonary function equipment, we can now offer you 12 entirely different units especially designed for this purpose.

This means that whatever your pulmonary function testing needs, there is a unit available to meet your requirements at a price you can afford to pay. Standard equipment is priced from a modest \$125.00 to a top of \$1925.00.

Collins also offers you a choice of 66 optional accessories for use with the above equipment. This gives you a selection of special valves, tubing, tonometers, meters and many other aids to enlarge the scope of routine testing or simplify scientific research.

A new 44 page catalog illustrates, describes and lists prices on all equipment and accessories. We'll send you a copy if you will ask for Catalog IM.

WARREN E. COLLINS, INC. 555 HUNTINGTON AVENUE BOSTON 15, MASS.

PSYCHIATRY IN GENERAL PRACTICE

By J. A. WEIJEL, M.D. Consulting Psychiatrist, Amsterdam

The helpful use of psychiatry in general practice is facilitated by the nonspecialist's use of the vast amount of knowledge already obtained by psychiatrists and psychonalysts. Based on recent applied research, this book gives a basis for using psychiatry with the majority of mentally normal patients. Every facet in the link between medical, psychological and social problems, including the approach to a patient and a patient's attitude toward treatment, is covered. Included is a sample psychosocial questionnaire to aid in bringing your psychological knowledge of a patient to the same level as your somatic information.

FREE EXAMINATION COUPON --ELSEVIER PRESS, INC., Dept. AIM

ELSEVIER PRESS, INC., Dept. AIM 126 Alexander St., Princeton, N. J.

Send me for 10 days FREE examination PSYCHIATRY IN GENERAL PRACTICE (Weijel). Within 10 days I will remit purchase price plus small delivery cost, or return book and owe nothing.

| Name | | ÷ | | | * | × 1 | | | × | | | | | × | | × | | | | | | | | | | | | * | | | | |
|------------------|--|---|--|---|---|-----|--|---|---|---|---|----|----|---|---|---|----|----|---|---|---|---|---|-----|---|-----|---|---|---|----|-----|---|
| Address | | é | | | | . , | | × | * | | | | | | è | | | | | | è | | × | K 1 | | | | | * | | | • |
| City | | * | | , | 8 | | | | | - | 2 | 30 | 16 | | | | 82 | št | a | e | | * | | | | | | * | | | . , | |
| Save! Same re | | | | | | | | | | | | | | | | | | | | | | | | p | ģ | n į | 5 | 0 | 0 | 51 | 5 | |

URGENTLY NEEDED

Back Issues of
ANNALS OF INTERNAL
MEDICINE

Due to a large demand for Vol. 48, No. 2 – February, 1958; Vol. 48, No. 5 – May, 1958; Vol. 49, No. 3 – September, 1958; Vol. 49, No. 4 – October, 1958; our stock for these issues has become completely exhausted.

We will pay \$.75 for good used copies.

Address Journals to:

E. R. LOVELAND, Executive Secretary 4200 Pine Street
Philadelphia 4, Pa.

Just Ready!

Today's best treatments for every disease you're likely to encounter

1959 CURRENT THERAPY



The newest of the uniquely helpful Current Therapy volumes brings you today's best treatments for more than 400 diseases.

Every method recommended is being used in practice today by the man who describes it. And each description was written *specifically* for this book. Each of the 305 contributors was selected by the Board of Consulting Editors as being eminently well qualified to discuss the treatment of a certain disease. All recommended treatments are approved by the Board as being the most effective available today.

You'll find that 282 of the treatments in this 1959 Volume are different and better in some way than the best treatment known last year for the same disease. Such new treatments as these are included: Ristocetin in treatment of bacterial pneumonia; Diuril in cirrhosis of the liver; Triiodothyronine in coma of hyperthyroidism; Diniazanine for thread-worm infection; Epinephrine and Isuprel in treatment of atrial flutter; etc.

By 305 American Authorities selected by a Board of Consulting Editors. Edited by Howard F. Conn, M.D. 781 pages, 8\frac{1}{2}" x 11". \$12.00. New!

New (4th) Edition-Duncan's Diseases of Metabolism

You'll find this a practical working guide on the latest techniques of diagnosis and treatment of the metabolic disorders that you frequently meet. Advances in the field have necessitated such drastic revisions for this New (4th) Edition that it is virtually a new book.

22 authorities simplify complex subjects and make them immediately applicable to your patients' problems. New help is given on such topics as: means of nourishing the anorexic patient; a simple bedside test to establish diagnosis of diabetic coma; hormones and obesity; the role of cholesterol; diagnostic procedures in puzzling cases of diabetes insipidus; the optimum use of the eight different insulins; etc.

Edited by Garfield G. Duncan, M.D., Professor of Medicine, University of Pennsylvania; Director of Medical Divisions, Pennsylvania Hospital and The Benjamin Franklin Clinic. With contributions by 22 Authorities. 1104 pages, 6¼"x 10", with 226 illustrations. About \$18.50.

New (4th) Edition-Just Ready!

| 1013 | W. B. SAUNDERS Company, West Washington Square, Please send me the following and charge my account: | AIM 3-59 Philadelphia 5 |
|----------|---|----------------------------|
| Caunat | □ 1959 Current Therapy | |
| Saunders | □ Duncan's Diseases of Metabolism | . About \$18.50 |
| | Name | |
| | | |
| | Address | |



ACID TYPES from the Gelusil Family Album

UNCLE MILO

By and large, ace firefighter Uncle Milo fed his ulcers per doctor's orders. But sometimes there he was... face to face with some forbidden delicacy. Then a single indiscretion, in a weak moment, was all it took to put him out of action.

Today, though, whatever the will-power of your ulcer patients, you can provide lastingly effective pain relief and acid control with Gelusil . . . the antacid adsorbent Uncle Milo should have had.

Especially important to your hospitalized patients . . . Gelusil is all antacid in action . . . contains no laxative . . . does not constipate. The choice of modern physicians, for every antacid need.

GELUSIL

the physician's antacid





"...safety and practicality...recommend its use in the treatment of shock."

SHOCK INJECTION

ARAMINE

BITARTRATE

a superior vasopressor with a choice of routes for optimal response—no tissue slough observed**

ARAMINE rapidly raises and maintains blood pressure in shock. Simplicity of administration with reported freedom from tissue slough, necrosis or thrombophlebitis^{1,4} encourages its prompt use. Patients respond with increased glomerular filtration rate, renal blood flow and urinary output. Vasopressor effect is smooth and sustained with no secondary fall in blood pressure and no tachyphylactic response to repeated injections.

Versatile ARAMINE is indicated in shock accompanying anaphylaxis, myocardial infarction, brain damage and infectious disease, as well as hypotension due to hemorrhage, surgery and other factors that lead to shock.

supplied in 1-cc. ampuls and 10-cc. vials (10 mg. per cc.).

references: 1. Am. J. M. Sc. 230:357, Oct. 1955.

2. Circulation 16:1096, Dec. 1957.

3. Circulation 13:834. June 1956.

4. J.A.M.A. 163:1482, April 20, 1957.

ARAMINE is a trademark of Merck & Co., Inc.



NEXT STOP



CHICAGO

Site of the Fortieth Annual Session of the American College of Physicians, convening April 20-24, 1959.

The color television control van shown above, which will be parked outside the Michael Reese Hospital, will transmit eight hours of closed-circuit color telecasting to the Conrad Hilton. You are cordially invited to attend these programs.

Chicago Medical Society • March 2-4 (completed)

Michigan Clinical Institute • March 11-13 (completed)

American College of Physicians · April 21-24

Ontario Medical Association • May 27-29

American Medical Association • June 14-19

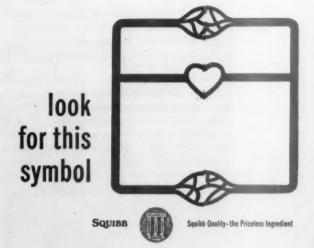


ANNIVERSARY 1949 1959

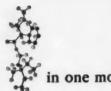
SKF MEDICAL COLOR TELEVISION

Smith Kline & French Laboratories

First in Medical Color Television



Please Mention this Journal when writing to Advertisers



three-way mechanism of action

A long step forward

MUREL

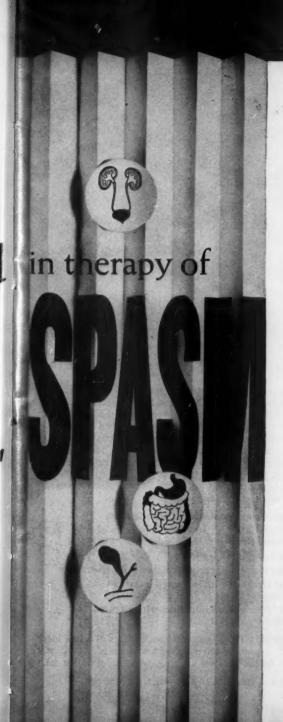
"MUREL" is the newest development of research in quaternary ammonium compounds. It advances today's therapy of G.U., G.I. and biliary tract spasm toward the ideal in decisive relief without intolerance or drug-induced complications. "MUREL" also supplements peptic ulcer therapy by breaking the chain reaction of spasm-pain.

Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of G.U. and biliary tract.

Supplied: "MUREL" Tablets—10 mg. Valethamate bromide, bottles of 100 and 1,000. "MUREL" Injectable—10 mg. per cc., vials of 5 cc. (Also available: "MUREL" with Phenobarbital Tablets—10 mg. Valethamate bromide with ¼ gr. phenobarbital per tablet, bottles of 100 and 1,000.)

Ayerst Laboratories . New York 16, N. Y. . Montreal, Canada





Three-Way Mechanism of Action in One Molecule

"MUREL" unites three mechanisms specific for smooth muscle spasmolysis: (1) anticholinergic inhibition of parasympathetic transmission, (2) musculotropic action with specific affinity for smooth muscle fibers, and (3) ganglionic blocking action at the synaptic level.

Precludes or Minimizes Untoward Side Effects

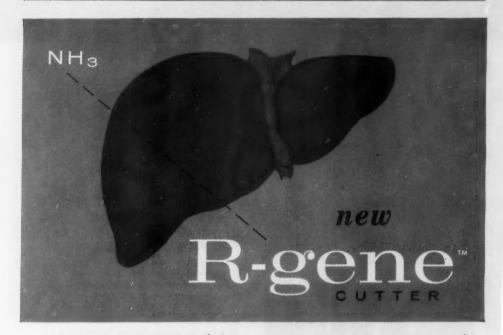
"MUREL" is especially well tolerated because:
(1) coordination of the three component actions permits significantly low dosages and also reduces reaction potential of any one mechanism,
(2) a natural specificity confines the anticholinergic action to the effector cells of smooth muscle,
(3) definite but transient ganglionic blocking action eliminates undesirable parasympathetic disturbances, (4) rapid detoxification and excretion prevent cumulative effect.

Widely Useful – Clinically Demonstrated

"MUREL" extends the clinical scope of dependable spasmolytic therapy, with indications ranging from mild to severe hypertonicity. In postoperative genitourinary spasm, cystitis and pyelitis—effective relief of pain and spasm was noted in all of 75 patients. In peptic ulcer—complete or substantial relief from the pain/spasm cycle was reported in 119 out of 127 patients. In biliary spasm and chronic cholecystopathies with or without stones—prompt, complete control of spasm was obtained in 20 out of 22 patients. 3

Peiser² states that even extremely strong convulsive abdominal pain and violent vomiting could be eliminated or substantially improved, and no unpleasant side effects or toxic reactions were noted at any time.

- 1. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.
- 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955.
- 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955.



helps reduce blood ammonia levels in hepatic coma

For maximum clinical effectiveness all measures to reduce ammonia intake, along with R-gene administration, should be started including reduction or withdrawal of protein intake, control of gastrointestinal bleeding, prompt removal of blood from the intestine, large oral doses of neomycin(from 4-12 Gm. daily) to reduce ammonia production in the intestine.

(The use of dextrose in conjunction with arginine apparently aids in the total ammonia utilization.) R-gene can reduce blood ammonia levels to shorten the duration of hepatic coma or to prevent impending hepatic coma. R-gene, a solution of L-arginine, accelerates the conversion in the liver of toxic ammonium to nontoxic urea.

Improvement of the mental status of patients in hepatic coma has been reported to accompany the reduction of blood ammonia levels usually within 24 to 48 hours following arginine therapy.*

R-gene is indicated in any disease states where elevated ammonia levels exert a toxic effect.

- in hepatic coma or impending hepatic coma
- in ammonia intoxication due to ingestion of ammonium salts
- in acute hepatic insufficiency
- following massive upper gastrointestinal hemorrhage
- in portal cirrhosis with increased intestinal nitrogenous contents
- in any hepatic encephalopathies with elevated blood ammonia levels

How Supplied: The R-gene package consists of a half liter Saftiflask® containing 400 cc. of a 5% solution of L-arginine, a 100 cc. Ambot® of 50% dextrose, and administration set.

*Najarian, J. S., and Harper, H. A.: Am. J. Med. 21:832 (Dec.) 1956.

Detailed literature is available from your Cutter man or write to Dept. 9-19C



CUTTER LABORATORIES

Berkeley, California



IMMEDIATE ACTION: KONAKION is a potent, prompt-acting synthetic vitamin K_1 (not an analog) which duplicates the physiologic activity of the natural vitamin.

MULTIPLE CHOICE OF ROUTES OF ADMINISTRATION: oral, intramuscular, or intravenous ... compatible with most I.V. vehicles, including isotonic saline solution, the usual dextrose solutions in distilled water or in saline, and Ringer's solution.

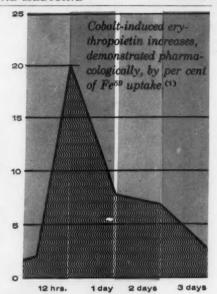
CONVENIENT LOW-DOSAGE FORMS: conforming to the present trend toward smaller doses in vitamin-K therapy... no waste, precise dosage administration.

NEW MARGIN OF SAFETY: substantially wider margin than that of the vitamin-K analogs. Capsules – 5 mg; Ampuls – 1 mg/0.5 cc KONAKION® – brand of phytonadione

NEW KONAKION

ROCHE LABORATORIES - Division of Hoffmann-La Roche Inc - Nutley 10, New Jersey

Activates the physiologic mechanism in anemia therapy



RONCOVITE-mf

Each tablet contains: Cobalt chloride (Cobalt as Co..3.7 mg.)..15 mg., Ferrous Sulfate, exsiccated..100 mg.

Only cobalt among therapeutic agents enhances production of erythropoietin to promote red cell formation. 1,2,3

With Roncovite-MF, increased erythropoietin production permits excellent hematopoietic response with sharply reduced iron dosage.

Cobalt-iron (Roncovite therapy) has been demonstrated as superior to iron alone in the common hypochromic anemias such as menstrual anemia, anemia of pregnancy, nutritional anemia of infancy and refractory anemias of chronic infection. 4.5,6,7,8

(1) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Pizak, L. F.: Blood I3:55 (Jan.) 1958. (2) Gurney, C. W.: Jacobson, L. O. and Goldwasser, E.: Ann. Int. Med. 49:363 (Aug.) 1958. (3) Korst, D. R.; Bishop, R. C. and Bethell, F. H.: J. Lab. & Clin. Med. 52:364 (Sept.) 1958. (4) Ausman, D. C.: Journal-Lancet 76:290 (Oct.) 1956. (5) Holly, R. G.: Obst. & Gynec. 9:299 (Mar.) 1957. (6) Holly, R. G.: Clin. Obst. & Gynec. I:15 (Mar.) 1958. (7) Diamond, E. F.; Gonzales, F., and Pisani, A.: Illinols M. J. II3:154 (April) 1958. (8) Hill, J. M.; La Jous, J., and Sebastian, F. J.: Texas State J. Med. 51:686 (Oct.) 1955.

LLOYD BROTHERS, INC.

·CINCINNATI 3, OHIO

nlw

Satisfactory modification of the manifestations of abnormal brain activity is often achieved with individual psychotropic drugs acting on a single sector of the brain. In many patients, however, and despite high dosages, or change to another agent, response is only partial and is associated with lethargy and other more undesirable by-effects. Investigators have postulated that agents which will simultaneously alter the activity of more than one sector of the brain might produce a more satisfactory modification of undesirable emotional and behavioral patterns, thereby promoting a greatly improved total patient-response. To test this theory investigators recently have administered a low dosage of promazine, a phenothiazine, with a low dosage of meprobamate. The enhanced beneficial response elicited by this low-dosage dual attack is provided by Prozine and warrants your consideration.

PROZINE

new agent

PROZINE

meprobamate and promazine hydrochloride, Wyeth

SPECIFIC CONTROL THROUGH DUAL ACTION

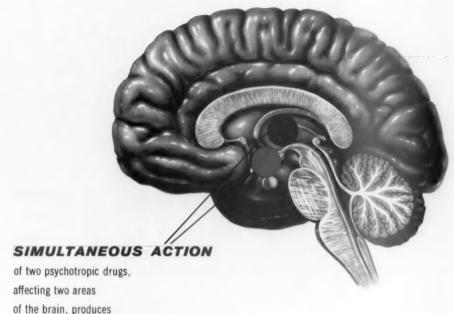
PROZINE controls anxiety and tension as well as motor excitability. This effect on the components of emotional reaction is possible because of the dual sites of action of PROZINE—the thalamic and hypothalamic areas of the brain. The unique dual action of PROZINE enables the physician to exert more specific control of emotionally disturbed patients. **PROZINE** is indicated in patients with a primary emotional disturbance,

in patients with emotional disturbance unrelated to their organic disease, and in patients emotionally disturbed by primary organic disease.

PROZINE controls moderate to severe emotional disturbance manifested by apprehension and agitation, insomnia, depression, nausea and vomiting, gastrointestinal disturbances, alcoholism, menopausal symptoms, or premenstrual tension.

PROZINE in the recommended dosage (1 or 2 capsules, 3 or 4 times daily) produces more specific control than is obtainable with high doses of other ataractic agents. The benefits of a low-dosage regimen are unmistakable.

*Trademark



more SPECIFIC CONTROL

thus

in emotionally disturbed patients on PROZINE the dose required is diminished to the point where the incidence of side-effects and toxicity reactions is minimal and the patient is calm, tranquil, and amenable to additional therapy, whether it be educational, medical, or psychiatric.

PROZINE



PROZINE

SPECIFIC CONTROL THROUGH DUAL ACTION

The physician will see many applications for Prozine in his day to day practice, particularly in overly apprehensive medical patients (including surgical and obstetrical cases) and in the management of emotional problems of children, adolescents and the aged; also in emotionally disturbed patients who receive little or no relief from analgesics, barbiturates, anticholinergics, antihypertensives, hormones (estrogens and corticoids). The dosages of these drugs may be dramatically reduced.

PROZINE—Bottles of 50 capsules. Each green and

PROZINE—Bottles of 50 capsules. Each green and white capsule contains 200 mg. meprobamate and 25 mg. promazine hydrochloride.

Comprehensive literature is available





Wyeth

Philadelphia 1 Pa

when oral tetracycline therapy is impractical-



Sumycin Intramuscular provides rapid, sustained antimicrobial activity, when coma, shock, fulminating infection or postoperative complications hamper administration of Sumycin in the oral form. Concentrations in the blood and tissues reach peak levels for immediate control of tetracycline-sensitive organisms in a broad range of infections.

For immediate therapeutic response — Sumycin Intramuscular with Xylocaine.* Single dose vials containing tetracycline phosphate complex (equivalent to 250 mg. tetracycline HCl), and single dose vials containing tetracycline phosphate complex (equivalent to 100 mg. tetracycline HCl).

SUMYCIN

INTRAMUSCULAR

WITH AILDONING

Tetracycline HCl equivalent (mg.)

Dackadind

Flexible dosage form

Capsules (per capsule).......250 mg. Half Strength Capsules (per capsule) 125 mg. Syrup (per 5 cc. teaspoonful)......125 mg. Aqueous Drops (per cc.).......100 mg. Bottles of 16 and 100 Bottles of 16 and 100 60 cc. bottle 10 cc. bottle with 'FLEXIDGE' dropper

SQUIBB



Squibb Quality-the Priceless Ingredient

SURVOIN & AND PLENOSSE ARE SQUISS TRADEMARKS BY M. & ASTER PHARMACEUTICAL PRODUCTS, MIC FOR LADGEAU

stop diarrhea

solves acute diarrheal disease problems...

- swiftly relieves symptoms rapidly destroys bacterial pathogens (bactericidal rather than bacteriostatic)
- succeeds where others fail against the enteric "problem pathogens" increasingly prevalent, refractory strains of Staphylococcus, Escherichia, Salmonella and Shigella

... without creating new problems

- does not upset the balance of normal intestinal flora
- does not encourage monilial or staphylococcal overgrowth
- does not induce significant bacterial resistance



A PLEASANT ORANGE-MINT FLAVORED SUSPENSION containing FUROXONE, 50 mg. per 15 cc., with kaolin and pectin For patients of all ages (may be mixed with infant formulas, passes through a standard nursing nipple) m Dosage: Should provide (in 4 divided doses) 400 mg. daily for adults, 5 mg./Kg. daily for children m Supplied: bottles of 240 cc. (also: FUROXONE Tablets, 100 mg. scored, bottles of 20 and 100)

THE NITROFURANS-a unique class of antimicrobials EATON LABORATORIES, NORWICH, NEW YORK

a specific treatment for a V. I.P.

your very important patient...
(and what one isn't!)

with a very important problem...

controlled by a very important product...
(Polaramine...the newest antihistamine)

The control of your patient's allergy is very important to her. She expects the greatest relief possible and she can have it with POLARAMINE.

Until Polaramine, your patient had to take the antihistamine benefits with the side effects. But now Polaramine—

the closest approach to a perfect antihistamine—
virtually eliminates side effects and achieves a greater therapeutic effectivene
in the management of a wide range of seasonal and nonseasonal
allergies at lower dosages than other antihistamines.

POLARAMINE REPETABS permit patients daylong or nightiong relief from allergic symptoms with a single medication.

Supplied: POLARAMINE REPETABS, 6 mg., bottles of 100 and 1000.

Tablets, 2 mg., bottles of 100 and 1000.

the first
major antihistamine advance
in over a decade . . .

POLARAMINE*

REPETABS

daylong or nightlong relief

SCHERING CORPORATION . Bloomfield, New Jersey

Schering



Tetracycline with Citric Acid Lederle

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York Coderle



iron your patients can tolerate

Rarical

iron-calcium

TABLETS

a unique new compound, ferrous calcium citrate, with tricalcium citrate

- · iron and calcium in one molecule
- · more hemoglobin in less time
- · no leg cramps with this iron-calcium



Another
reason
for
prescribing
predictable
weight reduction
and control!

A STRASIONIC RELEASE ANORETIC

RESIN

Max Insurance Company

SUMMARY OF SPECIFIC BIPHETAMINE ADVANTAGES

10-14 Hour Appetite Curb with Mildly Invigorating Action

Single Capsule Daily Dose

Balanced Caloric Intake and Energy Output

Predictable Weight Loss . . . a comfortable 1 to 3 lbs. a week in 9 out of 10 cases (Freed, S. Charles; Keating, J. W.; Hays, E. E.— Annals of Internal Medicine 44, 1136, June 1956)

Three Strengths-

Biphetamine 20 mg., 12½ mg., 7½ mg., each capsule containing equal parts of amphetamine and dextro amphetamine in the form of a resin complex

STRASENBURGH Originators of 'Strasionic' (sustained ionio) Release



R. J. STRASENBURGH CO. ROCHESTER, N. Y., U.S.A.

Now

in inflammatory anorectal disorders . . .

The Promise of Greater Relief

the first suppository to contain

hydrocortisons for effective control of proctitis

- Proctitis accompanying ulcerative colitis
- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis



Ulcerative Colitis



Radiation Proctitis



Postoperative Scar Tissue

Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth



Philadelphia 1, Pa.

SOON

accelerate convalescence with nutritional therapy

Sustagen°

Complete food, Mead Johnson powder

When you prescribe Sustagen during convalescence, you help fulfill the critical needs of your patients for increased amounts of calories, protein and vitamins. "In some instances of acute illnesses, injury, or surgery, intensive nutritional therapy may be the deciding factor in the outcome." Sustagen, because it generously supplies all known essential nutrients in convenient concentrated form, helps speed recovery.



Mead Johnson Symbol of service in medicine

There is a form
of short-acting
NEMBUTAL to serve
every need in
barbiturate
therapy



*when the oral route is not feasible

NEMBUTAL

(Pentobarbital, Abbott)

sodium suppositories

200 mg. (3 grs.)

120 mg. (2 grs.)

60 mg. (1 gr.)

30 mg. (1/2 gr.)

abbott

9000E

THE HEART DISEASE PATIENT NEEDS RELIEF FROM

EMOTIONAL STRESS



ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease." (Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.

(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown

meprobamate (Wallace)

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WWALLACE LABORATORIES, New Brunswick, N. J.

bu

os ph be

IS THIS YOUR PATIENT?



EARLY POSTMENOPAUSE

Complains of low back pain, vague aches and fatigue Posture is poor No x-ray evidence of bone lesions



LATER POSTMENOPAUSE

Back pain is severe, spreading to hips ("girdle pain") Patient is round shouldered, walks with a stoop X-ray reveals compression fractures of lower vertebrae





70 AND OVER

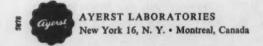
Fracture of hip after a minor fall X-ray reveals fracture of neck of femur X-ray reveals compression fractures of lower lumbar vertebrae

These three patients have osteoporosis. Early diagnosis and treatment with "Formatrix" is important because osteoporosis is probably the only age change that can be averted. With "Formatrix" therapy, relief from the symptoms of low back pain, vague aches and fatigue may be obtained in as little as a few weeks. "Formatrix" supplies the essential materials to stimulate increased bone formation and prevent further loss of bone substance that leads eventually to loss of height, stooped posture, and disabling fractures.

The highest incidence of osteoporosis may be found among the 14,000,000 women in the U.S.A. who are 55 years of age and over. Some investigators claim that almost all women past the menopause will show some degree of osteoporosis; furthermore, if all these women were examined carefully, 50 per cent would show x-ray evidence of decreased bone mass.

Suspicion may be the handiest diagnostic tool since presenting symptoms vary from mild to severe and incapacitating pain, and no x-ray evidence of spinal degeneration is available until about 30 per cent of the bone matrix is lost. Between these two extremes there are other signs of estrogen deficiency such as wrinkled and thinning skin, a tendency to appear older than stated years; there may also be hypercalciuria when postmenopausal osteoporosis is complicated by acute osteoporosis of disuse.

Osteoporosis is primarily an atrophic condition of bone matrix formation and any factor that depresses osteoblastic activity or retards the formation of protein and connective tissue such as prolonged immobilization, cortisone therapy, or malnutrition will favor development of osteoporosis in both male and female.





"FORMATRIX" contains three most essential bone building materials necessary for matrix formation, estrogen, androgen and vitamin C.

The estrogen component of "Formatrix" stimulates osteoblastic activity, thus aiding calcium and phosphorus deposition; it also imparts a feeling of "wellbeing." The anabolic action of methyltestosterone promotes the synthesis of protein and restores a positive

nitrogen balance. Together, these hormones have a greater effect on bone and protein metabolism than either alone, and side effects are minimized because of the opposing action of the two steroids on sex-linked tissues. Vitamin C plays an important role in formation of intercellular cement substance and amino acid synthesis. "Formatrix" has a large amount of vitamin C to aid in new bone matrix formation and to further help in the healing of fractures.

"FORMATRIX" - each tablet contains:

| Conjugated estrogens equir | e ("Premarin",) | 1.25 mg. |
|----------------------------|-----------------|----------|
|----------------------------|-----------------|----------|

LITERATURE AVAILABLE ON REQUEST



preingencone are and ated enorosis

bone

steo-

and

cornent

EARLY POSTMENOPAUSE No x-ray evidence of bone lesion

2.



LATER POSTMENOPAUSE

X-ray reveals compression fracture of lower vertebrae

3.



70 AND OVER

X-ray reveals fracture of neck of femur

TO RELIEVE LOW BACK PAIN - TO PROMOTE HEALING OF FRACTURES

in osteoporosis

FORMATRIX'

for matrix formation

(Brand of Steroid - Vitamin Combination)

Dosage: 1 tablet a day — In the female, three weeks of treatment with a rest period of one week between courses is recommended.

Supplied: Tablets, bottles of 60 and 500.



NOW...

FOR ADULTS - CHILDREN - INFANTS

A CONTRAST MEDIUM THAT
FULFILLS ALL THE
CRITERIA FOR
RADIOLOGIC EXAMINATION
OF THE
ALIMENTARY CANAL



- a true solution—permits delineation of gastric and duodenal mucosa, and identification of small ulcers
- does not inspissate-risk of residual hard masses eliminated; safe for use in the acutely ill and in cases of suspected or known obstruction
- ** minimal absorption—passes readily along alimentary tract with negligible absorption
- ** virtually nontoxic—safe on accidental, or deliberate, introduction into body cavities; may be used in post-anastomosis studies
- ** miscible with blood-allows detection of bleeding points and visualization of bleeding ulcers
- 2t low viscosity-permits demonstration of small fistulous connections, including tracheoesophageal fistulae in infants
- cathartic effect-eliminates delay in surgical procedures, or in serial or follow-up radiologic studies
- * well tolerated—side reactions minimal; contraindicated only in individuals with iodine sensitivity
- may be administered orally, by tube, or by rectum

SQUIBB New York 22, N. Y.

Squibb Quality — The Priceless Ingredient

Gastrografin, providing 76% sodium and methylglucamine diacetylaminotriiodobenzoates, is supplied in bottles of 120 cc. (4 fl. oz.).

"GASTROOMAPIN" IS A SQUISS TRADEHAR

A workhorse
"mycin"
for
common
infections



respiratory infections

prompt, high blood levels

consistently
reliable
and reproducible
blood levels

minimal adverse reactions

With well-tolerated CYCLAMYCIN, you will find it possible to control many common infections rapidly and to do so with remarkable freedom from untoward reactions. CYCLAMYCIN is indicated in numerous bacterial invasions of the respiratory system—lobar pneumonia, bronchopneumonia, tracheitis, bronchitis, and other acute infections. It has been proved effective against a wide range of organisms, such as pneumococci, H. influenzae, streptococci, and many strains of staphylococci, including some resistant to other "mycins." Supplied as Capsules, 125 and 250 mg., vials of 36; Oral Suspension, 125 mg. per 5-cc. teaspoonful, bottles of 2 fl. oz.



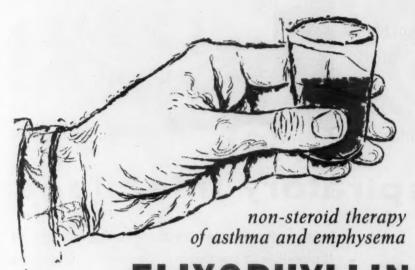
CYCLAMYCIN°

Triacetyloleandomycin, Wyeth



Conforms to Code for Advertising









Just as with I.V. aminophylline,* high theophylline blood levels reached in minutes - from a single dose.*



After absorption, theophylline is slowly eliminated. Therapeutic blood levels endure for hours.*



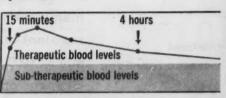
This predictability of blood levels permits quite constant therapeutic blood levels night and day, providing relief of wheezing, dyspnea, cough, and protection against acute attacks for most patients.*

DOSAGE: First two days:

45 cc. (three tbsp.) on arising; 45 cc. (three tbsp.) on retiring;

45 cc. (three tbsp.) once midway between above doses

(about 3 P.M.)



After two days of therapy the size of doses should be slightly decreased. Each tablespoonful contains: theophylline 80 mg., alcohol 3 cc. Prescription only - bottles of 16 fl. oz.

Detroit 11, Michigan

*Reprints of these studies on request.

NEW 2-PART PLAN FOR TREATMENT OF HYPERTENSION

First

for response within first 24 hours, start patients on

Harmonyl-N

The synergistic action of HARMONYL and NEMBUTAL produces, usually within the first 24 hours, a definite subjective response, so that patients enjoy calmer days, more restful nights while high blood pressure begins to fall. Each HARMONYL-N Filmtab combines 0.25 mg. of HARMONYL, Abbott's alkaloid of Rauwolfia canescens, with 30 mg. of NEMBUTAL Calcium . . . a standard in barbiturate therapy. Suggested dosage is 2 or 3 Filmtabs daily.

Filmteb-Film-scaled tablets, Abbett; pat. applied for

THEN, AFTER TWO TO FOUR WEEKS, WHEN RESPONSE IS ESTABLISHED ...



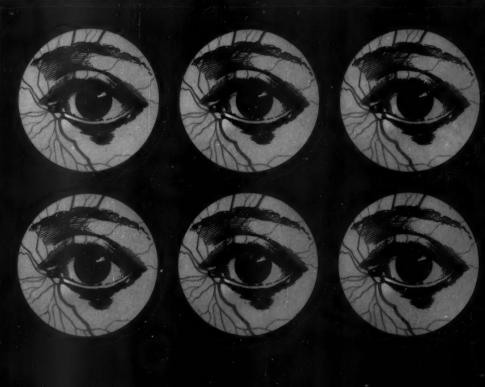
NEW 2-PART PLAN FOR TREATMENT OF HYPERTENSION

Second maintain improved blood pressure levels by switching patients to Harmonyl®

When initial tension is overcome and NEMBUTAL's sedation is no longer needed, regular HARMONYL will continue to keep blood pressure at desirable levels... yet won't hamper patients with an excess of side effects. Clinical tests have shown that HARMONYL produces significantly less daytime lethargy than reserpine or the alseroxylon fraction, while controlling blood pressure just as efficiently. Thus, if patients continue to work while under your care, they can work capably. HARMONYL is supplied as 0.1-mg., 0.25-mg. (grooved) and 1-mg. (grooved) tablets. Suggested dosage is 0.25 mg. once or twice a day.

C1988, ARROTT LABORATORIES, HORTH ENISARS, ILLINOI





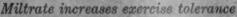
angina attacks

m ye effective thun ve odilators alone

Miltrate

MILTOWN° + PETN

The long-acting nitrate, PETN, helps
maintain normal myocardial metabolism
while Miltown relieves fear, anxiety and
tension. As a result, Miltrate controls
both physical and emotional causes
of angina attacks.



- reduces nitroglycerin dependence
- is notably safe for prolonged use
- provides convenient one-tablet dosage

Supplied: Bottles of 50 tablets.

Each tablet contains: 200 mg. Miltown + 10 mg. pentaerythritol tetranitrate.

Usual desage: 1 or 2 tablets q.i.d. before meals and at bedtime. Desage should be individualized.

References

- 1. Shapiro, S.: Observations on the use of meprobamate in cardiovascular disorders
 - Angiology 8:504, Dec. 1957.

 2. Friedlander, H. S.: The role of staraxics in cardiology. Am. J. Cardiol. 1:395.
 - 3. Eskwith, I. S.: The holistic approach to origina pectoris. Am. Heart 4. 33:521, April 1998.



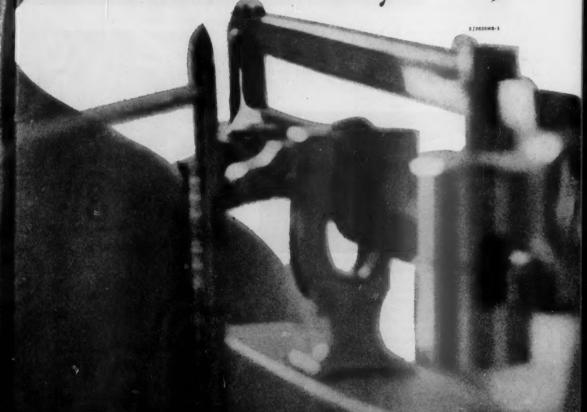
WALLACE LABORATORIES, New Brunswick, N. J.



The drug that lowered this patient's blood pressure for the first time without side effects is now available for your prescription...

Created by C I B A
World Leader in
Hypertension Research

here is the full story... please turn



a major improvement in rauwolfia a major advance in antihypertensive therapy

Developed after three years of basic research, proved during one of the most extensive clinical trials in pharmaceutical history, here is what **Singosero** can do:

Patient P. K. was first seen with a blood pressure of 220/138 mm. Hg; he complained of headache, palpitation, nervous tension and hyperhidrosis.



Hospitalized briefly for observation and treatment, he was placed on a 4-Gm. sodium diet, plus chlorothiazide and mecamylamine regulated according to b.p. reading, which he was taught to take himself.



One month later his blood pressure was 140/104; he complained of dryness of mouth, chest pain, constipation and nocturia (twice a night). He was then started on Singoserp (0.5 mg. daily) with instructions to reduce the other medications to the extent possible, as evidenced by his b.p. readings.



After five months on Singoserp the patient's blood pressure ranged between 120/84 and 140/100. No mecamylamine was required; only ½ the original dose of chlorothiazide was required. One month later, chlorothiazide was stopped and the patient was maintained on Singoserp alone, 1 mg. b.i.d. Favorable blood pressure response continues and patient feels well. Since taking Singoserp patient reports no chest pain, no mouth dryness, no other side effects.



2/20361

ne of ere is

tment,

ding to

Singoserp' (syrosingopine CIBA)

Solves the Side Effects Problem in Most Hypertensive Patients

1. For new hypertensive patients Singoserp is the ideal antihypertensive drug for new patients because it lowers blood pressure without creating the side effects problem posed by conventional rauwolfia agents.

2. For hypertensive patients already undergoing drug treatment Singoserp, added to any antihypertensive regimen, makes it possible to maintain blood pressure levels achieved with more potent agents, while reducing their dosage requirements—or even eliminating them altogether in some cases.

Infrequent side effects —"The chief advantage of [Singoserp] over other Rauwolfia derivatives seems... to be the relative infrequency with which it produces disturbing side effects."¹

Less sedation -"It [Singoserp] is approximately equipotent to reserpine as a hypotensive agent but is definitely less sedative or tranquilizing."²

Depression relieved -"In those patients who had been depressed, [Singoserp] was substituted for other Rauwolfia preparations and within a period of one to two weeks this depression was relieved."³

Created in the laboratory by altering the reserpine molecule so as to preserve its antihypertensive property and virtually eliminate its undesirable side actions.

Dosage: In New Patients: Average initial dose, 1 to 2 tablets (1 to 2 mg.) daily. Some patients may require and will tolerate 3 or more tablets daily. Maintenance dose will range from ½ to 3 tablets (0.5 mg. to 3 mg.) daily. When necessary for adequate control of blood pressure, more potent agents may be used adjunctively with Singoserp in doses below those required when they are used alone. In Patients Taking Other Antihypertensive Medication: Add 1 to 2 Singoserp tablets (1 to 2 mg.) daily. Dosage of other agents should be revised downward to a level affording maximal control of blood pressure and minimal side effects.

Supplied: Singoserp Tablets, 1 mg. (white, scored); bottles of 100.

References: 1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: To be published. 2. Wolffe, J. B.: Mod. Med. 26:253 (Feb. 1) 1958. 3 Bartels, C. C.: To be published.

C I B A

2/2838HK-4

in Mexico, it's called the 'turista' or 'Montezuma's revenge'



diarrhea by any name

GASTROENTERITIS
BACILLARY DYSENTERY
PARADYSENTERY
SALMONELLOSIS
DIARRHEA OF THE NEWBORN
NONSPECIFIC DIARRHEA
"SUMMER COMPLAINT"

usually responds rapidly to

Cremomycin. RECHTCH-SULFASUXIDINE®-KAOLIN-PECTIN SUSPENSION

for rapid relief of all diarrheas-regardless of etiology

fruit-flavored, readily accepted by patients of all ages*

Neomycin—rapidly bactericidal against most intestinal pathogens, but is relatively ineffective against such diarrhea-causing organisms as Shigella.

SULFASUXIDINE—an ideal adjunct to neomycin because it is highly effective against Shigella and certain other neomycin-resistant organisms.

Kaolin and Pectin—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

*For infants, CREMOMYCIN may be administered in the regular bottle feeding, since its fine particles easily pass through a standard nursing nipple.



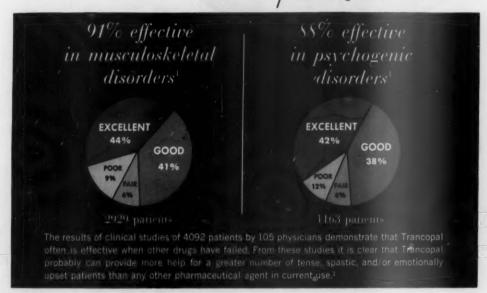
MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILA. 1, PA.

CREMONYCIN AND SULFASURIDINE ARE TRADEMARKS OF MERCE & CO., INC.

for <u>low back pain, torticollis, bursitis</u> and <u>anxiety states</u>¹³

Trancopal

the first true tranquilaxant*/ MUSCLE RELAXANT TRANQUILIZER



better tolerated and safer than older drugs

- Lower incidence of side effects than with zoxazolamine, methocarbamol or meprobamate.
- · No known contraindications. Low toxicity.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.
- No perceptible soporific effect, even in high dosage.

Desage; Usual adult dose, 1 Caplet (100 mg.) three or four times daily. Children (from 5 to 12 years), ½ Caplet (50 mg.) three or four times daily.

Supplied: Trancopal Caplets® (peach colored, scored) 100 mg., bottles of 100 and 1000.

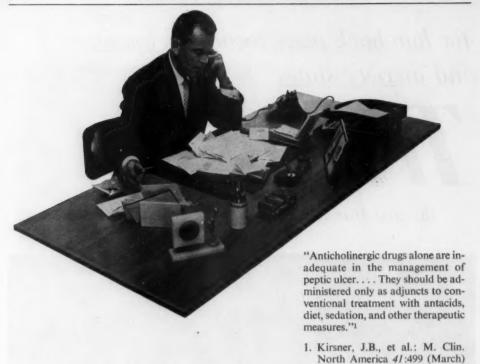
References: 1. Cooperative Study, Department of Medical Research, Winthrop Laboratories - 2. Lichtman, A. L.: Kentucky Acad. Gen. Pract. J. 4-28, Oct., 1958 - 3. Baker, A. B.: Medicin Mcd., 26:140, April 15, 1958.

*tran-qui-lax-ant [< L. tranquillus, quiet; L. laxure, to loosen, as the muscles]

Winthrop LABORATORIES

1340-N

Trancopal (brand of chlormethazzonee) and Capluta, trademarks reg. U.S. Pat. Off.



In peptic ulcer: six aids

to total management

ALUDROX SA is not only an effective anticholinergic, but also an antacid, sedative, demulcent, anticonstipant, and pepsin-inhibitor. Thus, one convenient preparation satisfies six requirements of total peptic-ulcer therapy.

An important new anticholinergic of demonstrated usefulness, ambutonium, is responsible for the potent antisecretory and antimotility properties of ALUDROX SA.

ALUDROX® SA*

Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide, and Butabarbital, Wyeth

* Sedative and Anticholinergic

SUPPLIED: SUSPENSION, bottles of 12 fl. oz. TABLETS, bottles of 100. Each teaspoonful (5 cc.) and tablet contains 2.5 mg. of ambutonium and 8 mg. of butabarbital combined with aluminum hydroxide and magnesium hydroxide approximating 1 teaspoonful of aluminum hydroxide gel and 1/4 teaspoonful of milk of

magnesia. Also available: Tablets Ambutonium Bromide, 10 mg., bottles of 100.



Philadelphia I, Pa.

Thorazine*

(chlorpromazine, S.K.F.)

one of the fundamental drugs in medicine

'Thorazine' is a valuable therapeutic agent in nearly all fields of medicine because of its three fundamental properties:

- capacity to alleviate anxiety, tension and agitation without dulling mental acuity
- profound antiemetic effect
- · ability to potentiate narcotics and sedatives

Available: Tablets, Spansule* <u>sustained release</u> capsules, Ampuls, Multiple dose vials, Syrup and Suppositories.

Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off.



Butazolidin

tablets · alka capsules

potent · nonhormonal · anti-inflammatory agent

BUTAZOLIDIN tablets or the Aika capsules are equally effective but individually adaptable in a wide range of arthritic disorders.

Recent clinical reports continue to justify the selection of Butazolidin for rapid relief of pain, increased mobility, and early resolution of inflammation.

Gouty Arthritis: "...95 per cent of patients experienced a satisfactory response..."

Rheumatoid Arthritis: In "A total of "...8.6 per cent complete remissions, 215 cases...over half, 50.7 per cent 47.1 per cent major improvement, 20.0 showed at least major improvement, per cent minor improvement..."

with 21.8 per cent showing minor improvement...." Osteoarthritis: 301 cases showed "...a total of 44.5 per cent with complete remission or major improvement. Of the remainder, 28.2 per cent showed minor improvement..." Spondylitis: All patients "...experienced initial major improvement that was maintained throughout the period of medication." Painful Shoulder Syndrome: Response of 70 patients with various forms showed "...8.6 per cent complete remissions, 47.1 per cent major improvement, 20.0 per cent minor improvement..."

References: 1. Graham, W.: Canad. M. A. J. 79:634 (Oct. 15) 1958.
2. Robins, H. M.; Lockle, L. M.; Norcross, B.; Latona, S., and Riordan, D. J.: Am. Pract. Digest Treat. 8:1758, 1957. 3. Kuzell, W. C.; Schaffarzick, R. W.; Naugler, W. E., and Champlin, B. M.: New England J. Med. 256:388, 1957.

Availability BUTAZOLIDIN® (phenylbutazone egro): Red coated tablets of 100 mg. BUTAZOLIDIN® Alka: Capsules containing BUTAZOLIDIN® (phenylbutazone egrey), 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide, 1.25 mg.

geigy ARDSLEY, NEW YORK

02959

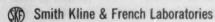
relief from the suffering and mental anguish of

cancer

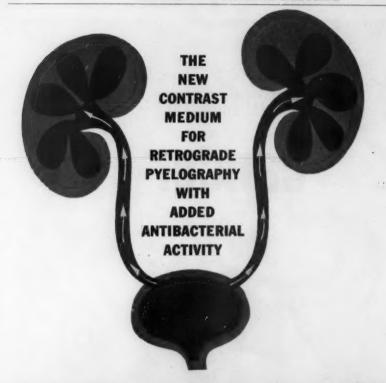


THORAZINE* (chlorpromazine, S.K.F.)

one of the fundamental drugs in medicine



*T.M. Reg. U.S. Pat. Off.



RETROGRAFIN

Squibb Sodium and Methylglucamine Diatrizoates and Neomycin Sulfate

for maximum opacification when urinary tract infection is present or suspected Retrografin provides the same excellent film quality...exceptional patient toleration...and optimal convenience in retrograde pyelography as that provided by Renografin 30%. And, in addition, it contains 2½% neomycin (as the sulfate) for widely effective bactericidal action in cases with proved or suspected urinary tract infection.

Supplied in 50 cc. vials

Retrograde pyelography with either Retrografin or Renografin 30% is especially useful when poor kidney function makes other procedures impractical, or when retrograde study will provide supplemental diagnostic information. for routine retrograde pyelography

RENOGRAFIN 30%

Souibb Sodium and Methylglucamine Diatrizoates

Its excellent local tissue tolerance and proved systemic tolerance, even in the presence of pyelo-renal backflow, make Renografin 30% the preferred agent for routine, optimal density retrograde pyelograms.

Supplied in 50 cc. vials



Squibb Quality-the Priceless Ingredient

"RETROGRAPIN" AND "REMOGRAPIN" ARE SQUIRE TRADEMARKS

for prompt and sustained relief from severe mental and

emotional stress



THORAZINE* SPANSULE† capsules

30 mg. 75 mg. 150 mg. 200 mg. 300 mg.

Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F. †T.M. Reg. U.S. Pat. Off. for <u>sustained release</u> capsules, S.K.F.

He gets the facts for doctors

Preston Parrish, B.S. in Pharmacy, has attended many training sessions to sharpen his knowledge as a Wyeth detail representative. A 1955 graduate in pharmacy studies at the Medical College of Virginia, Mr. Parrish came to Wyeth with experience as a retail pharmacist, as well as with a background in the U.S. Army Medical Service Corps.

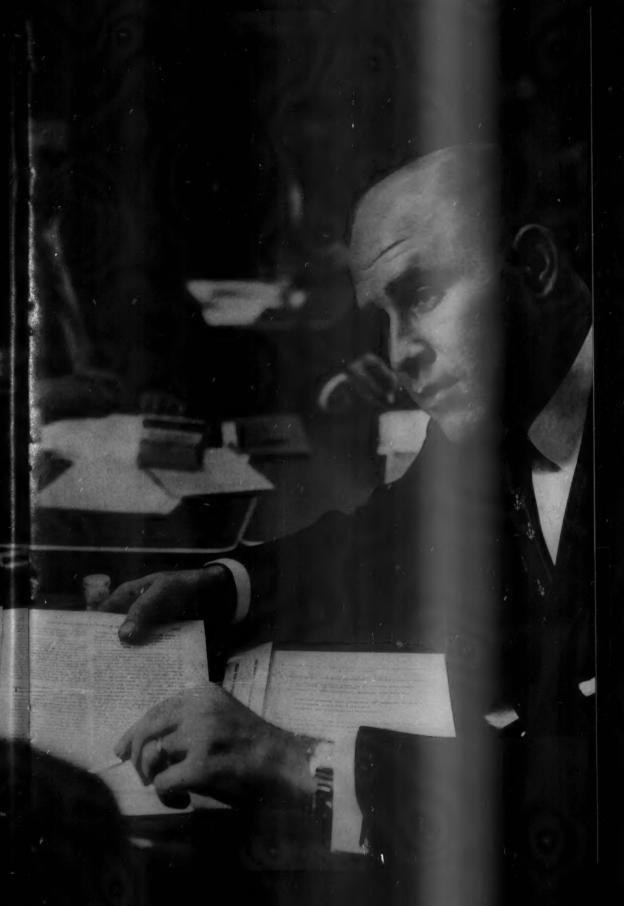
Preston Parrish typifies the high-caliber men that Wyeth and other pharmaceutical houses are searching for. His primary function is to be useful to physicians. He is alert, conscientious, well grounded.

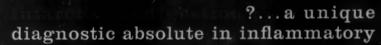
Right now, like his associates shown here, all of whom are liberal arts or science degree holders, he is being schooled in new facts and in how to convey them concisely to busy doctors. For a full day, he has been absorbing information about an important drug.

He has been exposed to the most modern teaching techniques. He has heard reports from technical and medical personnel on research, pharmacology, toxicity, and clinical experience. He has seen demonstrations. He has questioned and been questioned. He has filled pad after pad with notes. Soon he will go home for still further study.

Men like Preston Parrish are selected for what they are and what they bring. Their effective training as detail representatives is a constant feature of Wyeth service to the medical profession. It is a training that never ends.







or necrotic states C-reactive protein, a molecular abnormality of serum, is of particular diagnostic value in acute myocardial infarction of any degree acute rheumatic fever, widespread malignant disease and bacterial infections. A simple antigen-antibody precipitin test accurately indicates its presence.

C-Reactive Protein Antiserum, Schieffelin

a positive always indicates pathology

... no range of normal values. not influenced by varying blood properties... not affected by medication.

The C. R. P. A. test is semi-quantitative—intensity of precipitin reaction parallels intensity of disease process at any stage. It is the earliest and most reliable measure of the effectiveness of therapy in control of inflammation or necrosis.

The C. R. P. A. test requires less than 2 minutes to set up in the laboratory or physician's office. A qualitative reading may be obtained within 10 minutes. Complete instructions and bibliography available on request

Schieffelin V. Co. Since 1794 4 3 New York 3, New York

NEW

anticholinergic / antispasmodic / tranquilizer A SENTRY FOR THE G.I. TRACT



Since G.I. disorders present multiple difficulties, perhaps you will welcome one medication that combats the most prominent and most troublesome symptoms.

ENARAX protects against

hypermotility hyperemotivity

hypersecretion hyperirritability

ENARAX combines a new long-acting anticholinergic (antisecretoryantispasmodic1) with the proven antisecretory-tranquilizer2-8 (ATARAX®) to relieve pain, spasm, hyperacidity and disease-induced tension. Just two tablets daily proved clinically effective in 428 out of 490 patients with a wide variety of gastrointestinal disorders. 1.2.7

Selective postganglionic action on the G.I. tract minimizes side effects. Of 512 patients treated to date, reactions were usually mild, transient and easily reversed. Mouth dryness, blurring of vision, dizziness, urinary hesitancy either disappeared with continued use or were controlled by reducing the dosage.



ENARAX one tablet at breakfast one tablet at bedtime

full-time relief in

peptic ulcer functional bowel syndrome ulcerative colitis biliary tract dysfunctions gastritis gastroenteritis pylorospasm cardiospasm duodenitis hiatus hernia (symptomatic) genitourinary spasm dysmenorrhea

Each ENARAX tablet contains:
Oxyphencyclimine HCl... 10 mg.
Hydroxyzine HCl (ATARAX *)... 25 mg.

Dosage: One-half to one tablet twice daily – preferably in the morning and before retiring. The maintenance dose should be adjusted according to therapeutic response. Use with caution in patients with prostatic hypertrophy or glaucoma.

Supplied: In bottles of 60 black-and-white scored tablets.

References: 1. McHardy, G., et al.: Paper presented at Postgraduate Course in Gastroenterology, University of California School of Medicine, San Francisco, California, January 27, 1958. 2. Strub, I. H., and Carballo, A.: To be published. 3. Schuller, E.; Gaz. des Hôpitaux 10:391 (Apr. 10) 1957. 6. Farah, L.; Internat. Rec. Med. 169:579 (June) 1956. 5. La Barre, J.: Compt. rend. Soc. Biol. (Paris) 150:1807 (Oct.) 1956. 6. Harrisson, J. W. E., et al.: Paper presented at the 4th Pan-American Congress of Pharmacy and Biochemistry, Washington, D. C., November 3-9, 1957. 7. Data in Roerig Medical Department files.



New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being



is a arthea.

adsorptive power

CLAYSORB

KAOLIN

CLAYSORB is 5 times as adsorptive as kaolin

When you prescribe POLYMAGMA or POLYMAGMA Plain to control diarrhea, you are prescribing adsorptive superiority. Both preparations contain Claysorb—a new intestinal adsorbent whose superiority over kaolin has been demonstrated in exhaustive studies.^{1,2,3}

For bacterial diarrhea, POLYMAGMA is bactericidal to many intestinal pathogens. It is soothing and protective to the irritated mucosa. It aids in the restoration of normal intestinal function. Highly effective, highly palatable.

For nonbacterial diarrhea, POLYMAGMA Plain—same formula but without antibiotics.

Barr, M., and Arnista, E.S.: J. Am. Pharm. A. (Scient. Ed.) 46:493 (Aug.) 1957.
 Barr, M., and Arnista, E.S.: *Ibid.* 46:486 (Aug.) 1957.
 Barr, M.: *Ibid.* 46:490 (Aug.) 1957.

Polymagma

Dihydrostreptomycin Sulfate, Polymyxin B Sulfate, and Pectin with Claysorb* (Activated Attapulgite, Wyeth) in Alumina Gel

Wyoth

(n) in Alumina Gel Philadelp

*Trademark

This advertisement conforms to the Code for Advertising of the Physicians' Council for Information on Child Health

Please Mention this Journal when writing to Advertisers

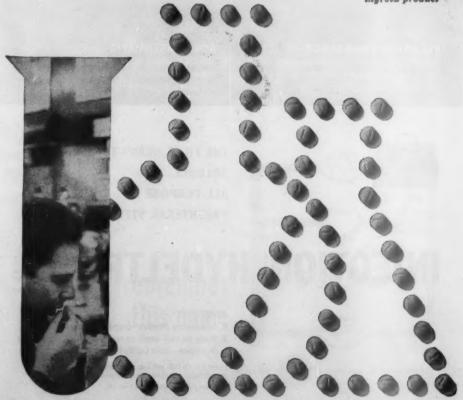
THE PIONEER manuf. IN in hype THYROID dis STANDARD-IZATION

Armour thyroid tablets assure: Consistent response—unsurpassed quality—highest manufacturing standards—full potency up to 17 years of storage—dependable therapy in: frank thyroid deficiencies and when hypothyroidism is associated with chronic recurrent colds, functional menstrual disorders, sterility, habitual abortion, obesity, hypometabolism. Thyroid is recommended in long-term therapy with ACTH or corticosteroids. Supplied in \(\frac{1}{4}, \frac{1}{2}, 1, 2 \) and 5 grain strengths.

specify ARMOUR THYROID



the most
widely prescribed
thyroid product



ARMOUR PHARMACEUTICAL COMPANY · KANKAKEE, ILLINOIS / a leader in biochemical research

YOUR PATIENT?



ALLERGIC EMERGENCY-INJECTION



ACUTE ASTHMATIC - INJECTION HYDEL-



In your bag... ready for use. IMMEDIATELY!

PARENTERAL STEROID

INJECTION HYDELTRASOL

THE FIRST READY-TO-USE,

ADVANTAGES:

SOLUBLE, **ALL-PURPOSE**

- 1. Immediately effective-dramatic response in minutes
- 2. Ready for use-needs no reconstitution or refrigeration
- 3. In solution-flows readily through a small-bore needle

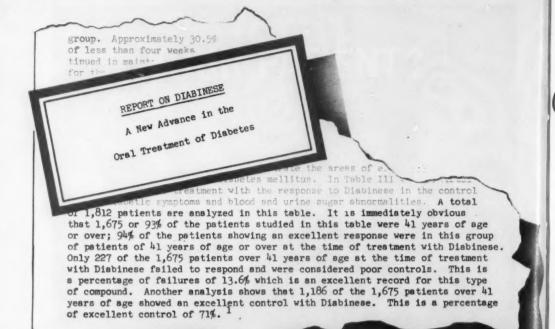
SUPPLIED: In 2-cc. and 5-cc. vials, each cc. containing 20 mg. of prednisolone 21-phosphate as the di-sodium salt. Hydoltracel is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME DIVISION OF MERCK & CO., Inc., Philadelphia 1, Pa.





BAUTERY IS A SQUIRE TRADEMARK.



An advance in potency of therapeutic activity



An advance in duration of therapeutic activity



An advance in effectiveness over a wider range of patients



DIABINESE®

brand of chlorpropamide

once-a-day dosage

a MAJOR ADVANCE in the ORAL treatment of DIABETES

PFIZ

MORE EFFICIENT ORAL CONTROL IN MATURITY-ONSET DIABETES

Diabinese exerts a hypoglycemic effect within one hour, which becomes maximal within three to six hours. It exhibits twice the potency of tolbutamide on acute administration and up to six times its potency on chronic administration. Most patients can be started on only 0.25 to 0.5 Gm. daily given as a single dose with breakfast.

Diabinese has a longer biologic half-life than tolbutamide. Excreted slowly, 80 to 90 per cent of one administration is eliminated in 96 hours. A single dose provides a therapeutic effect lasting 24 hours or longer. Since it remains in the blood as the active hypoglycemic material and is only gradually removed, Diabinese affords longer-lasting clinical benefit, with relatively constant blood levels, on low, once-a-day dosage.

The enhanced potency and duration of effectiveness of Diabinese is reflected in its notable record of clinical success in properly selected patients. Ninety-four per cent of excellent responses to Diabinese are in the most common group - the "maturity-onset" diabetics. Diabinese proved effective in 86.4 per cent of 1,675 patients over 40 years of age. Good results have even been obtained in some "brittle" diabetics, as well as in many patients exhibiting primary or secondary failure with tolbutamide.

DOSAGE: IMPORTANT - Patients should not be given starting doses in excess of 0.5 Gm. daily. An initial dosage of 250 mg. daily is recommended for geriatric diabetics. For full details see Section 8 of Report on Diabinese.

SUPPLIED: 250 mg. tablets, scored; bottles of 60 and 250. 100 mg. tablets, scored; bottles of 100.

> REPORT ON DIABINESE Your personal bound copy is available from your Pfizer representative.



Science for the world's well-being

PFIZER LABORATORIES Division, Chas, Pfizer & Co., Inc., Brooklyn 6, New York





MODANE for constipation

MODANE doesn't leave your patient stranded on the road to Recovery with no help for the flaccid, atonic bowel. Modane takes him all the way through RELIEF and REHABILITATION.

MODANE's danthron provides prompt, positive relief — without irritation or griping — acts systemically to stimulate only the large intestine. But more! — MODANE's pantothenic acid favors revitalization of the atonic bowel — stimulates the body's formation of a normal supply of acetylcholine, so essential for optimal peristalsis.

Prescribe MODANE — the deconstipant which relieves and helps rehabilitate.

THREE FORMS

Tablets Regular (yellow), Tablets Mild (pink), and Liquid. Each Tablet Regular contains 75 mg. danthron (1.8-dihydroxyanthraquinone) and 25 mg. calcium pantothenate. Each Tablet Mild and teaspoonful Liquid contains 37.5 mg. danthron and 12.5 mg. calcium pantothenate.

DOSAGE

One tablet, one teaspoonful or fractional teaspoonful, immediately after the evening meal.



THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO

Dallas . Chattanooga . Los Angeles . Portland

RELIEVES NERVOUSNESS



ANXIETY AND TENSION often complicate management of allergic patients. In such cases, the "psychogenic component...must be treated before clinical improvement can be expected."†

When tranquilization with Miltown was added to conventional therapy in asthma, allergic headache, hay fever, urticaria, angioneurotic edema and gastrointestinal allergy with emotional components, many resistant patients definitely improved.†

(†Eisenberg, B. C.: Role of tranquilizing drugs in allergy. J.A.M.A. 163:934, March 16, 1957.)

Miltown causes no adverse effects on respiratory functions, nasal secretions, intestinal motility, or other autonomic functions.

Miltown[®]

Available in 400 mg. scored and 200 mg. sugarcoated tablets.

Also available as MEPROSPAN* (200 mg. meprobamate continuous release capsules) and MEPROTABS* (unidentifiable 400 mg. meprobamate sugar-coated tablets).

CH-7706



WALLACE LABORATORIES, New Brunswick, N. J.

protects against anginal attacks

the most effective drug currently available for prolonged prophylicite treatment of anging pertoris." Prevents space 30% of anging attacks.



eases cardiac tension

RUSSEK: "I favor ATARIX [as the tranquiller for the anxious cardiac] ... because there is an absence of side offects with this drug, and also because in cardiacs who are troubled with estopic beats, ATARAN has a Emini-dine-like action."



CARTRAX

(PETN + ATARAX)

Dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. FETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. FETN plus 10 mg. ATARAX).

For convenience, write "CARTRAX 10" or "CARTRAX 20."

Supplied: In bottles of 100.

References: 1. Russek, H. I.: Postgrad. Med. 19:502 (June) 1956. 2. Russek, H. I.: Presented at the Symposium on the Management of Cardiovascular Problems of the Aged, Dade County Medical Association, Mismi Beach, April 12, 1968.



New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being

*TRADEMARI

WHY RISK DELAYED RECOVERY FROM

ENTERITIS?

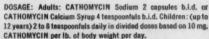
Staphylococcic enteritis and other serious staph infections among hospitalized patients may be refractory to all antibiotics except CATHOMYCIN (novobiocin). For such infections, CATHOMYCIN constitutes an ideal antibiotic. It has an established record* of effectiveness against strains of organisms resistant to most other antibiotics. When administered in combination with other antibiotics, CATHOMYCIN protects against the emergence of resistant strains.

CATHOMYCIN produces therapeutic blood levels quickly—usually maintaining these levels for 12 hours or more. The drug does not destroy beneficial intestinal flora. It is generally well tolerated and shows no evidence of cross-resistance with other antibiotics.

CATHOMYCIN

for staphylococcic septicemia, enteritis, postoperative wound infections and other serious staph infections.

NOVOBIOCIN



SUPPLIED: Capsules sodium novobiocin, each containing the equivalent of 250 mg. of novobiocin—vials of 16 and 100—and as an orange-flavored syrup (aqueous suspension), in bottles of 60 cc. and 473 cc. (1 pint). Each 5 cc. CATHOMYCIN Syrup contains 125 mg. (2.5%) novobiocin, as calcium novobiocin.

*Complete bibliography available on request.



For Parenteral Therapy LYOVAC® CATHOMYCIN



MERCK SHARP & DOHME Division of MERCK & CO., INC., Philadelphia 1, Pa.



'CARDILATE' SUBLINGUAL TABLETS



ANGINA PECTORIS

"Nitroglycerin and erythrol tetranitrate when administered sublingually are among the most effective of all prophylactic agents available for the treatment of patients with angina pectoris. The comparatively prolonged duration of action of erythrol tetranitrate makes it especially valuable for clinical use."

Riseman, J. E. F., et al.: Circulation 17:22, 1958



Sublingual administration obviates inactivation of nitrites in gastrointestinal tract.



Most closely approximates nitroglycerin in frequency and degree of effectiveness.

'Cardilate' brand Erythrol Tetranitrate Sublingual Tablets 15 mg., scored.



BURROUGHS WELLCOME & CO. (U.S.A.) INC. Tuckahoe, New York in the common cold and other upper respiratory infections

first in preference
for relief from cough
quiets the cough and
calms the patient

PHENERGAN®

EXPECTORANT

Promethazine Expectorant, Wyeth with Codeine Plain (without Codeine)

expectorant • antihistaminic sedative • topical anesthetic

NEW NON-NARCOTIC FORMULA

Pediatric PHENERGAN Expectorant with Dextromethorphan, Wyeth



full-range symptomatic relief
plus prevention of secondary infection

PEN · VEE · Cidin

Penicillin V, Salicylamide, Promethazine HCI, Phenacetin, Mephentermine Sulfate, Wyeth

antibacterial • analgesic • antipyretic antihistaminic • mood-stimulating

A WORLD

OF USEFULNESS

The world-wide acceptance of "Mysoline" is amply supported by the work of more than 100 investigators in 15 different countries. This effective anticonvulsant for control of grand mal and psychomotor attacks is well tolerated. Side effects, when they occur, are usually mild and transient, and no irreversible toxic effects have been reported. Four years of successful clinical use in the United States further confirms the effectiveness and safety of "Mysoline."

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000

AVERST LABORATORIES . NEW YORK 16 NEW YORK . MONTREAL CANADA

"Mysofine" is available in the United States by arrangement with Imperial Chemical Industries, Ltd



"... the digitalis preparation of choice for the treatment of the usual patient with congestive heart failure ..."*

GITALIGIN"

WIDEST SAFETY MARGIN—AVERAGE THERAPEUTIC DOSE ONLY 1/4 THE TOXIC DOSE.

FASTER RATE OF ELIMINATION THAN DIGITOXIN OR DIGITALIS LEAF.

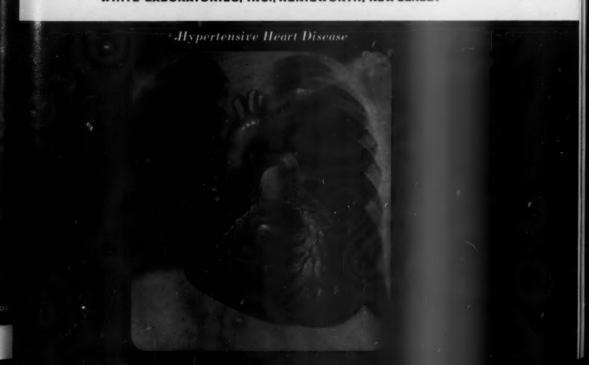
THESE SIMPLE DOSAGE EQUIVALENTS MAKE IT EASY TO SWITCH YOUR PATIENT TO GITALIGIN—0.5 mg. of Gitaligin is approximately equivalent to 0.1 Gm. digitalis leaf, 0.5 mg. digoxin or 0.1 mg. of digitoxin.

Supplied:

GITALIGIN 0.5 mg. Tablets—bottles of 30 and 100.
GITALIGIN Injection Ampuls—2.5 mg. in 5 cc. sterile, I.V. solution.
GITALIGIN Drops 30 cc. bottle with special calibrated dropper.

*BATTERMAN, R. C., ET AL.: CIRCULATION 5:201, 1982
TWHITE'S BRAND OF AMORPHOUS GITALIN . \$BIBLIOGRAPHY AVAILABLE ON REQUEST

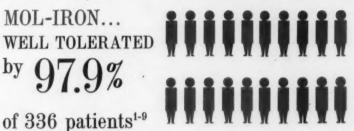
WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY



FOR UNMATCHED TOLERANCE AND OPTIMAL ABSORPTION

MOL-IRON...

of 336 patients1-9



But 22.4% G. I. side effects with FeSO.

VITAMIN C-"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid..."10

MOL-IRON

WITH VITAMIN TABLETS

KENILWORTH, NEW JERSEY

The effect of Unitensen (cryptenamine) on 21,913 hypertensive patients

Summary of the experiences of 2,082 physicians in private practice.

A continuation of "Proof In Practice."

Safe, Dependable Office Management For Most Hypertensive Patients

The "Proof In Practice" study validates, in day-to-day private practice, the effectiveness of Unitensen products (cryptenamine) as reported in clinical trials in hospitals and institutions. It proves that Unitensen affords well tolerated, dependable office management for the majority of hypertensive patients. Unitensen effectively lowers blood pressure . . . improves renal and cerebral blood flow . . . exerts no adverse effects on circulation . . . and is free of serious side effects. The results of the Study are shown in Table 1.

Table 1.

| No. of Patients | Results | Percent |
|--------------------|----------------|---------|
| 6,822 | Excellent | 31.1% |
| 11,201 | Good | 51.1% |
| 2,802 | Fair | 12.8% |
| 1,088 | Unsatisfactory | 5.0% |
| 622 | Side effects | 3.0% |

Basic Hypertensive Therapy

Although many of the patients in the Study also received diuretics and/or tranquilizers during the course of treatment, it was noted that the vasodilating effect of Unitensen was required to obtain optimum blood pressure control. Unitensen, a true hypotensive agent is potentiated by diuretics. A combination of the two is frequently recommended for lower dosage of each drug, minimizing the side effects of either.^{1,2,3,4}

UNITENSEN-R®

Each tablet contains cryptenamine (tannates) 1.0 mg., reserpine 0.1 mg.

UNITENSEN-PHEN®

Each tablet contains cryptenamine (tannates) 1.0 mg., phenobarbital 15 mg.

UNITENSEN®

Each tablet contains cryptenamine (tannates) 2.0 mg.

Clinical supplies available upon request.

Bibliography:

- Cohen, B. M.: "The Ambulatory Patient with Hypertension: An Approach to Office Management" Presented: American Medical Association Convention, San Francisco, California, June 22-27, 1958.
- 2. Freis, E. D.: South. M.J. 51:1281-1288 (Oct.) 1958.
- Gifford, R. (Mayo Foundation): "Combined Drug Therapy of Hypertension . . . Methodology of Treatment" Presented: Symposium on Hypertension, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania, December 8-12, 1995.
- 4. Finnerty, F. A., Jr. (Georgetown University): "Treatment of Hypertension Associated with Toxemia of Pregnancy" Presented: Symposium on Hypertension, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania, December 8-12, 1958.

Irwin, Neisler & Co. Decatur, Illinois



"Antacid? Rorer's Maalox. It doesn't constipate and patients like its taste better ... By the way, try their new double strength Tablet Maalox No. 2. It's great!"

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

Tablet Maalox No. 2: 0.8 Gram, double strength (equivalent to two teaspoonfuls), Bottles of 50 and 250.

Samples on request.

WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

Please Mention this Journal when writing to Advertisers

1959

more than tetracycline alone



MYSTECLIN-V
G O N T A I N S
MYC OSTATIN
FOR A SPECIFIC DEFENSE
AGAINST SEGONDARY MONILIAL SUPERINFECTION
Mysteclin-V protocts patients against
antibiotic induced intestinal moniliasis.
This protoction is provided by Mycostatin,
the antifungal antibiotic, with specific action against Candida
(Monilia) albicans.²

BOTH ARE OFTEN NEEDED WHEN BACTERIAL INFECTION OCCURS

SQUIBB TETRACYCLINE PHOSPHATE COMPLEX (SUMYCIN) AND MYSTATIN (MYCOSTATIN)

Capsules (250 mg./250,000 u), bottles of 16 and 100. Haif-strength Capsules (125 mg./125,000 u), bottles of 16 and 100. Suspension (125 mg./125,000 u per 5 cc.), 2 oz. bottles. Padiatric Brops (100 mg./100,000 u per cc.), 10 cc. dropper bottles. References: 1. Crunk, G. A.; Naumann, D. E., and Casson, K.; Antibiotics Annual 1957-1958, New Yark, Medical Encyclopedia Inc. 1958, p. 397 * 2. Newcomer, V. D.; Wright, E. T., and Sternberg, T. N. Antibiotics Annual 1964-1955, New York, Medical Encyclopedia Inc., 1955, p. 686.



tter t!"



Squibb Quality-the Priceless Ingredient

CHARLES OF THE PROPERTY OF THE PARTY OF THE

40TH ANNUAL SESSION

AMERICAN COLLEGE OF PHYSICIANS

CHICAGO

April 20-24, 1959

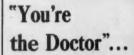


Enjoy extra care at no extra fare? Choose luxunious First Class, or economical Air Coach. Radar on every plane. Fast, dependable scheduled times to suit your convenience on the convention route of the nation. Ask your travel agent to give you full details along with his suggestions for combining your convention along with one of the many vacations available on United Air Lines. Or call your nearest United Air Lines office.





Ann Woodward, Director





EXCEPT when You're the Patient!

PREOCCUPIED with Patients A, B, C, D, etc., etc.? Leaving your own health care chiefly to chance, an iron constitution, "next year," or "some day, perhaps"? Recreation—one vacation in time to "save nine"—may be the answer. And you can positively plan for needed leisure from the day you select a qualified assistant and begin his indoctrination.

The Woodward Bureau has initiated many such satisfactory relationships to fortify and extend practice, lift a share of the load from the over-burdened successful physician, and provide that life-saving vacation-in-time.

May we help you in the search for The Right Man? We offer nationwide contacts, years of professional knowbow, a swift and systematic notification system. Write "today" and we'll be helping you "tomorrow."



Founders of the counseling service to the medical profession, sewing medicine with distinction over half c century. welcome relief of spasm and pain is continuously reported in functional G-I disorders, such as irritable, spastic colon syndrome; peptic ulcer; biliary dyskinesia; pylorospasm; and infant colic.

sure

relief can be expected . . . even in patients where other antispasmodics have failed. 1-3

direct dual antispasmodic action is specific to the G-I tract. Spasm pain is relieved by direct relaxation of the smooth muscle and postganglionic parasympathetic nerve blockage.

Safe even in the presence of glaucoma*... BENTYL does not increase intraocular tension, produce blurred vision, dry mouth or urinary retention.

relief of g-i spasm&pain Description of the second of the

Bentyl

20 mg. t.i.d. (dicyclomine) Hydrochloride

Chamberlain, D. T.: Gastroenterology 17:224, 1951.
 Heek, C. W.: J.M.A., Ga. 43:124, 1951.
 Canad. M.A.J. 69:532, 1953.
 Cholst, M., Goodstein, S., Eerens, C., and Ginotti, A.:
 A. M.A. J. 46:1924.
 150.



THE WM. S. MERRELL COMPANY

How York - CHICHENATI - St. Thomas, Catarlo

Anther Extents Protect of Original Married Research

Charles Street

DSA

proven in researchosa cosa cosa cosa cosa cosa

- COS1. Highest tetracycline serum levels 2000 COSA COSA COSA OSA COSA COSA COSA
- COS2. Most consistently elevated serum levels tosa COSA COSA COSA
- 3. Safe physiologic potentiation with a natural human metabolite

- cosproven in practice osa cosa cosa cosa cosa COSA COSA COSA COSA COSA COSA
- COS4. Rapid clinical response * SCOSA GOSA COSA COSA COSA COSA Unexcelled toleration (A. O. O. SA COSA COSA COSA COSA
- COS COSA COSA COSA COSA COSA COSA

capsules • oral suspension • pediatric drops

Pfizer Science for the world's well-being

Pfizer Laboratories Division, Chas. Pfizer & Co., Inc.

"... the most satisfactory form of treatment to date."

SIXTOIC will be saved.²

1. Briller, S. A.: M. Clin.
North America 41:1619, May, 1967.
2. Tatator, M. L.: Bol. Ame.
and Purto Rice 47:205, Aug., 1955.
increase in survival rate

Only 5 per cent of patients in severe coronary shock survive with conventional treatment. With Levophed 1 out of 3 patients

with life-saving



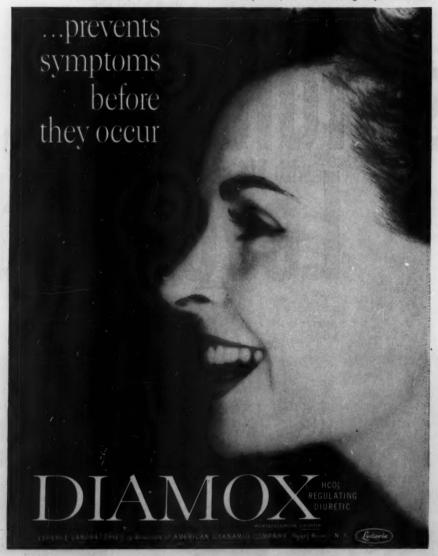
Levophed (brand of levarterenol), trademark rag. U. S. Pat. Off.

dynamic in premenstrual tension

Unlike tranquilizers, sedatives and analgesics, DIAMOX controls premenstrual tension by direct physiologic action. Working at the electrolyte level, DIAMOX gently mobilizes fluid and prevents accumulation in body tissue.

The usual pattern of tension and discomfort is simply overcome by a single DIAMOX tablet each morning for 6 to 10 days before menstruation.

Supplied: Scored tablets of 250 mg.; syrup containing 250 mg. per 5 cc. teaspoonful; and vials of 500 mg. for parenteral use.



FOR PRACTICAL MANAGEMENT OF HYPERTENSION

NEW

A SINGLE PROTOVERATRINE ALKALOID potent...safe...and an important addition to "combination therapy"

The isolation of pure, crystalline protoveratrine A* makes available, for the first time, a single chemically standardized veratrum alkaloid. Now, blood pressure can be lowered with doses smaller than ever before possible in oral veratrum therapy.

In Protalba-R[†] Tablets, protoveratrine A (0.2 mg.) is combined with reserpine (0.08 mg.)—providing two effective hypotensive agents with constant, unvarying potency. In contrast to complex alkaloid mixtures which have uncertain activity, the effects of Protalba-R are predictable and reproducible.

Used alone, Protalba-R can produce a significant decrease in both systolic and diastolic pressure. And, it is the logical supplement to therapy when hypertension cannot be controlled by diet modification and psychogenic measures or the use of tranquilizers and diuretics.

protalba-R

Supplied in bottles of 100 coss-scored tablets

*Patent Pending

†Trademark

PITMAN-MOORE COMPANY



SUGGESTIVE KEY...

for the problem of faulty fat metabolism



LECITHIN

RG Lecithin suggests itself as worthy of trial for persons with degenerative disease susceptibility brought on by their inability to metabolize fat with the efficiency of youth. RG Lecithin, refined from soybeans, is a dietary source of choline, inositol, and phosphorus, and is rich in essential unsaturated fatty acids. 2.

Mode of Administration

Available in either granular or wafer form, RG Lecithin is pleasant to take plain, or crumbled in juices or foods. Usually prescribed daily dosage: granules, 1 to 3 tablespoonfuls; 3 to 5 wafers.

Sale3.

No harmful side effects.

"Lecithin in Health and Disease,"

a brochure describing the product and its application, as well as the rationale for the use of "RG" Lecithin in the diet, is available to the medical profession upon request to Medical Consultant at the address below.

 Wittcoff, H., The Phosphatides; A.C.S. Monograph Series #112; Reinhold Pub. Corp. NYC 1951, p. 366-423. 2. Bloor, W. R., Blochemistry of the Fatty Acids; A.C.S. Monograph Series #93, Reinhold Pub. Corp. NYC 1943. 3. Article, Lecithin in the Diet; Journal A.M.A. 168:1168 (Oct. 25) 1958.



Central Soya Company, Inc.

1825 N. Laramie Avenue

Chicago 39, Illinois

Reported results with RONIACOL in intermittent claudication



FROM MALF A BLOCK TO TWO MILES. The patient, a 57-year-old white male with peripheral arteriosclerosis of about three years' duration, complained of pain in the right leg after walking half a block. After four weeks of treatment with Roniacol (75 mg per day), he was able to walk 20 blocks—and later two miles—without a sign of intermittent claudication. Three years after discontinuing therapy, "he still is able to walk unlimited distances and is without need of treatment."

CONVEXTED TO PURE VITAMIN IN THE 800Y. Roniacol is not an adrenergic blocking agent; it is converted to the pure vitamin form (nicotinic acid) in the body and acts directly on the smooth muscle of the vascular wall.

EMINENTLY SAFE. There are no known contraindications to Roniacol. "Patients up to the ages of ninety have tolerated the drug in doses up to 600 mg with no adverse effects." "

*M.M. Fisher and H.E. Tobrock: New York State J. Mod. \$3:63, 1953.

Roniacol

RONIACOL®-brand of beta-peridyl carbinol

Available in scored 50-mg tablets, bottles of 100, 500, and 1000. Romiacol Elixir, containing 50 mg of Romiacol per teaspoonful (5 cs), available in bottles of 16 ounces and one gallon.

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc
Nutley 10, New Jersey

for depression

'Deprol'

Clinically confirmed in over 2,500 documented case histories.

CONFIRMED EFFICACY

Deprol

- acts promptly to control depression without stimulation
- restores natural sleep and reduces depressive rumination and crying

DOCUMENTED SAFETY

Deprol is unlike amine-oxidase inhibitors

- ➤ does not adversely affect blood pressure or sexual function
- no excessive elation; no liver toxicity

Deprol is unlike central nervous stimulants

- ▶ does not cause insomnia or depress appetite
- ▶ no amphetamine-like jitteriness; no depression-producing aftereffects

1. Alexander, L.: Chemotherapy of depression—Use of moprobemate combined with benactyzine (2-diethylemineethyl benzilata) hydrochloride. J.A.M.A. 166:1019, Merch 1, 1986.

Literature and samples on request

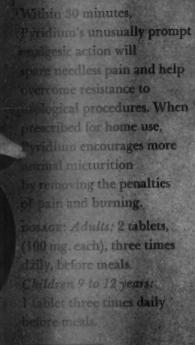
WALLACE LABORATORIES, New Branswick, N. J.

Beenge: Usual starting doce is I tablet q.i.d. When necessary, this does may be gradually increased up to 8 tablets q.i.d.

Composition: Each (ablet contains 400 mg, moprobamate and 1 mg, 2-diethylaminoothyl henrilate hydroshloride (benactyrine HCI).

Supplieds Sottles of 10 secred tablets.

-



eedless finary



PYRIDIUM®

(brand of chemisze-damino-pyridine)

"...the
emergency
transfusion
fluid
of
choice"*

ALBUMISOL

Normal Serum Albumin (Human)

No risk of serum hepatitis

Ready for administration; no storage problems

Human protein; readily metabolized

Contains no blood-clotting components

No grouping, typing, cross-matching required

Supplied: 'ALBUMISOL' 5%—In 250 and 500 cc. bottles in packages with a set of disposable intravenous equipment.

Also supplied: 'ALBUMISOL' 25% (Sait-Poor)—in 20 cc. bottles; in 50 cc. bottles in packages with a set of disposable intravenous equipment.

disposable intravenous equipment.

*Janeway, C.A.: Quart. Rev. Med. 9:153 (Aug.) 1952.



MERCK SHARP & DOHME

Division of MERCK & CO., Inc.
Philadelphia 1, Pa.



Pyridium Tri-Sulfa combines the efficacy of the classic triple sulfas with the full analgesic dosage of Pyridium. Relief of pain is prompt—within 30 minutes—and therapeutic sulfonamide levels are obtained within hours.

FORMULA:

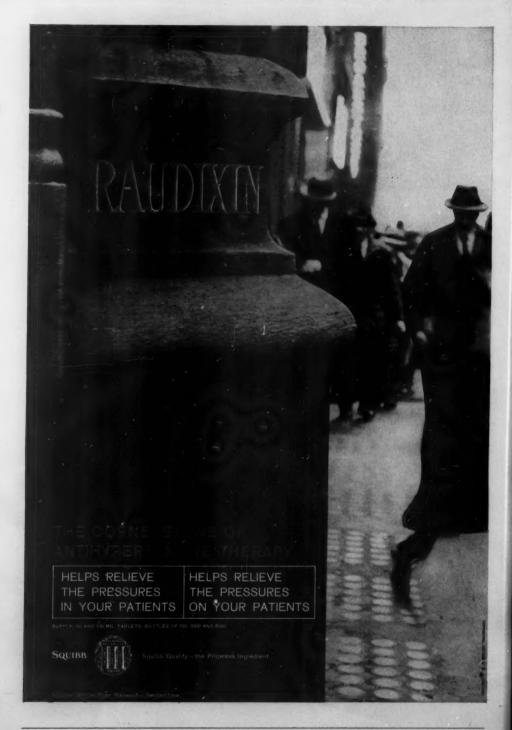
Pyridium, 150.0 mg. (2½ gr.); (brand of phenylazo-diamino-pyridine HCl) Sulfadiazine, 167.0 mg. (2½ gr.); Sulfamerazine, 167.0 mg. (2½ gr.); Sulfamethazine, 167.0 mg. (2½ gr.).

DOSAGE: Adults: 1 tablet four times daily.



PYRIDIUM° TRI-SULFA

(phenylazo-trisulfapyrimidine



Please Mention this Journal when writing to Advertisers

Mandelamine's therapeutic distinction stems from its ability to control chronic urinary infections, including those resistant to antibiotics.

Mandelamine suits all age groups but it is particularly useful in older patients. Its antibacterial action is confined to the urinary tract; sensitization is unlikely; no fluids or alkalies are needed and cost is most economical.

DOSAGE: Adults: Average

posage: Adults: Average initial dosage is 1.0 to 1.5 Gm. four times daily. Children over five: 0.5 Gm. four times daily.



MANDELAMINE"



Napoleon exhibited ulcer symptoms through most of his adult life, yet he scorned medication for his everlasting "spasms of nervous origin." He ignored his infirmities with violent naïveté despite an intense interest in medical science. Thus, the classic hand-incoat pose may have been the result of his paroxysms of gastric pain that sliced "like the stab of a penknife."

When your patient is besieged with an ulcer, Robins provides you with an armamentarium sufficient to repel it.

frontal assault - If your tactics dictate Local Action, try ROBALATE, which is dihydroxy aluminum aminoacetate (0.5 Gm. per tablet or 5 cc.), an antacid of definitely superior efficacy.

encirclement - If you prefer to approach the ulcer Systemically, prescribe

linergic-antispasmodic-sedative with the timetested natural belladonna alkaloids and phenobarbital, a veteran campaigner without peer. FORMULA: hyoscyamine sulfate, 0.1037 mg.; atropine sulfate, 0.0194 mg.; hyoscine hydrobromide, 0.0065 mg.; and phenobarbital (1/4 gr.), 16.2 mg.

multi-pronged attack - If you relish the strategy of combining antacid and antispasmodic-anticholinergic effects, use DONNALATE. It combines one-half of a DONNATAL tablet with one ROBALATE, ideal allies for comprehensive ulcer therapy.

Victory will be yours.

A. H. ROBINS CO., INC. • RICHMOND, VA.

ulcer Systemically, prescribe DONNATAL, the anticho-DONNATAL Robins





in alcoholism1.2

ACUTE EMERGENCIES - a single intramuscular injection of 50 mg. (2 cc.) Vistaril Parenteral Solution is usually sufficient to calm the patient and initiate sound sleep. Vistaril is exceptionally well tolerated. Antiemetic action and absence of respiratory depression are among valuable assets reported.

REHABILITATION -oral administration of 100-400 mg. daily in divided doses provides psychothera-peutic action which maintains calm and confidence, and promotes anxiety-free abstinence. The remark-able safety of Vistaril is reassuring in long-term maintenance.



1. Premature Ventricular Contractions



2. Paroxysmal Auricular Tachycardia



3. Paroxysmal Ventricular Tachycardia



Science for the world's well-being

e

Brooklyn 6, N. Y. Division, Chas. Pfizer & Co., Inc.

REFERENCES: 1. Miller, R. F.: Clinical Review, Vol. 1, No. 2 (July) 1958. 2. Van Gasse, J. J.: Clinical Medicine, 5:177-181 (Feb.) 1958. 3. Burrell, Z. L., et al.: Am. J. Cardiol., 1:624 (May) 1958. 4. Hutcheon, D. E., et al.: J. Pharmacol. & Exper. Therap., 118:461 (Dec.) 1956.

in arrhythmias 3,4

Many types of cardiac arrhythmias respond promptly to oral, intra-muscular or intravenous Vistaril therapy. Vistaril is particularly effective in ventricular extrasystoles, paroxysmal tachycardias (both auricular and ventricular), and ventricular extrasystoles complicat-ing auricular fibrillation. The following dosage regimen is recommended:

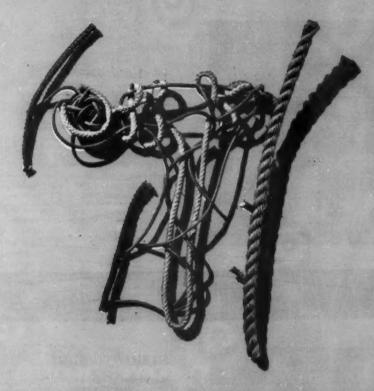
PARENTERAL DOSAGE: 50-100 mg. (2-4 cc.) I.M. stat., and q. 4-6 h. p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

IN ACUTE EMERGENCY, 50-75 mg. (2-3 cc.) I.V. stat.; maintain with 25-50 mg. (1-2 cc.) I.V. q. 4-6 h. p.r.n.

ORAL DOSAGE: Initially, 100 mg. daily in divided doses until arrhythmia disappears. For maintenance or prophylaxis, 50-75 mg. daily in divided doses.

SUPPLY: Vistaril Capsules, 25 mg., 50 mg. and 100 mg. Vistaril Parenteral Solution, 10 cc. vials, and 2 cc. Steraject®
Cartridges, each cc. containing 25 mg. hydroxyzine hydrochloride.

*Trademark



PYELONEPHRITIS

In pyelonephritis, "the tubules suffer from damage to their lining cells which show cloudy swelling, granular degeneration and diminution in size. Inflammatory cells and colloid casts are found in the lumen of the tubules. Inflammatory cells are present also in the interstitial tissue. The glomeruli remain normal over a long period."



In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

In the treatment of pyelonephritis, it is important to select an agent such as Furadantin which-in addition to its glomerular filtration-is secreted by the tubule cells. On the other hand, it has been demonstrated that sulfonamides, both free and acetylated, are excreted primarily by glomerular filtration,2 and that "the mechanism of excretion of tetracycline is solely a glomerular filtration process without tubular involvement."3

In pyelonephritis ... FURADANTIN, first

Furadantin "may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants. The importance of an agent with these characteristics that could be used for a long period in the treatment of chronic pyelonephritis has been recognized, and it is in this sphere that nitrofurantoin may have its greatest use."4

Available as Tablets, Oral Suspension.

ses: 1. Smith, I. M., and Lenye, L.: Am. Practitioner 9:78, 1958. 2. Bass, A. D.: Chemotherapy rist infections II: Sulfonamides, in Drill, V. A., ed.: Pharmacology in Medicine, New York, MIII Book Ce., Inc., 1954. 3. Pindell, M. H., et al.: J. Pharm. Exp. Ther. 122:61A, 1958. ren, B. A., and Crewley, W.: A.M.A. Arch. Int. M. 93:653, 1955.

NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides LABORATORIES, NORWICH, NEW

WHATEVERSTHE ETIOLOGY-EDEMA OF ANY DEGREE RESPONDS TO DUBLE



An unparalleled record of safety and efficacy.

DIURIL has proved to be highly effective in overcoming edema associated with a wide variety of fluid retention states including: hypothyroidism, menopausal syndrome, allergy, peripheral phlebitis, arthritis, migraine headache, ascites or peripheral edema due to malignant tumor, and obesity. In the last case, Landes and Peters¹ achieved excellent to good results in nine obese patients in whom overweight was associated with moderate or severe fluid retention.

1 Landes, R. P. and Peters, M. Postgrad, Med. 23:648, June 195

dosage: one or two 500 mg, tablets of DIURIL once or twice a day.

supplied: 250 mg, and 500 mg, scored tablets DIURIL (Chlorothiazide); bottles of 100 and 1000

DIURIL is a trademark of Merck & Co., Inc.

1959 Merck & Co., Inc.

Trademarks outside the U. S.

CHLOTRIDE, CLOTRIDE, SALURIC.

any indication for diuresis is an indication for DIURIL

reduces anginal attacks and fear of attacks

protects against pain by sustained coronary vasodilatation and control of complicating and triggering emotions

reduces fear of attacks
reduces severity of attacks
reduces frequency of attacks
reduces dependence on nitroglycerin
increases workload tolerance

Supplied: Tablets, vials of 50. Each tablet contains 200 mg. of meprobamate and 10 mg. of pentaerythritol tetranitrate.

BOUANTERATE

Meprobamate and Pentaerythritol Tetranitrate, Wyeth



Philadelphia 1 Pe

d

De

do

A CIBA Documentary Report

How clinicians evaluate the safety and effectiveness of RITALIN° as a psychic stimulant

| CONDITIONS TREATED | RESULTS | COMMENTS ON SAFETY |
|--|--|--|
| Depression accompanying chronic illness and convalescence from short-term illness; mild depression induced by life pressures; overtranquilization. | "The drug gave a plateau type of stimulation, smooth onset, with no euphoria The effect lasted about four hours, gave the patient a feeling of well-being" | "The side effects of Ritalin are minimal." "The work showed that the drug had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia." |
| Lethargy, fatigue and emotional depression secondary to chronic illness in elderly patients; mild depression secondary to short-term illness. (Twenty-three "normal," healthy people also received the drug.) | "For the entire 112 patients 66 per cent showed marked improvements [obvious drug effect and mood improvement]" | "No serious side reactions were noted In no case was it necessary to stop the drug. No evidence of significant effect upon blood pressure or pulse has been found. This is particularly interesting, since these side effects have been common with other mood elevating drugs"2 |
| Drug-induced psychophysiologic depression; physiologic after-effects of certain anesthetics; barbiturate intoxication; moribund states due to systemic infection. (All patients were epileptic, mentally retarded and/or brain damaged.) | "All except two [of 129] patients responded to the initial injection [of parenteral Ritalin] within 1½ to 15 minutes." | "In no instance was there any evidence of untoward effects." " the very poor basic physical condition of our patients in this study, those associated with profound chronic brain damage, accentuates the safety of parenteral Ritalin" |

DOSAGE: Oral: Dosage will depend upon indication and individual response. Many patients respond to 10 mg. b.i.d. or t.i.d. Others will require 20-mg. doses. In a few cases, 5-mg. doses will be adequate. If inability to sleep is encountered, last dose should be given before 6 p.m. Parenteral: 10 to 30 mg., intravenously or intramuscularly. RITALIN● hydrochloride (methylphenidate hydrochloride CIBA)

REFERENCES: I. Natenshon, A. L.: Dis. Nerv. System 17:392 (Dec.) 1956. 2. Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey 55:55 (Feb.) 1958. 3. Carter, C. H., and Maley, M. C.: Dis. Nerv. System 18:146 (April) 1957.

C I B A

AN AMES CLINIQUICK"

CLINICAL BRIEFS FOR MODERN PRACTICE

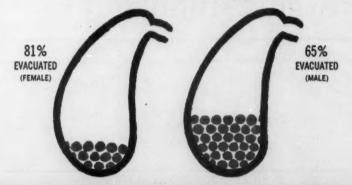
how do age and sex influence evacuation of the gallbladder?

Children and pre-adolescents, especially boys, have a faster emptying rate than adults. After puberty, the gallbladder of the male is slower in emptying—elderly women have a faster gallbladder evacuation rate than elderly men.

*Source: Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, vol. 2, p. 1178.

GALLBLADDER EVACUATION IN THE ELDERLY*

30 minutes after meal of egg volk



true hydrocholeresis plus reliable spasmolysis...

DECHOLIN with Belladonna

- · relieves the pain of smooth-muscle spasm
- · steadies the "nervous gut"
- · facilitates biliary and pancreatic drainage

available: Decholin with Belladonna Tablets: dehydrocholic acid, Ames 3¾ gr. (250 mg.) and extract of belladonna ¼ gr. (10 mg.). Bottles of 100 and 500.

for free-flowing "therapeutic bile"...

DECHOLIN'

(dehydrocholic acid, AMES)

- medical and postoperative management of biliary tract disorders
- routine physiologic support for geriatric patients
- constipation—natural physiologic laxation without catharsis
 available: DechoLin Tablets: dehydrocholic acid, Ames 3¾ gr. (250 mg.).
 Bottles of 100, 500 and 1000; drums of 5000.

AMES
COMPANY, INC
Elikhert - Indiana
Teranta - Canada



64788

normal bowel
function requires
intestinal contents
of proper consistency

KONSYL

A vegetable concentrate of naturally occurring hemicelluloses

Provides just the moist, smooth, effective bulk so essential to normal peristalsis. It precipitates formed stools in cases of simple constipation and non-specific diarrhea. It hastens the rate of improvement in irritable colon cases. It contains no artificial or irritating substances and is calorie-free. Furthermore, KONSYL is available at significantly lower-cost-to-patient prices. So . . .



Made by BURTON, PARSONS & COMPANY, Since 1932
Originators of Fine Hydrophilic Colloids
Washington 9, D. C.

NO is sy



Your patients will say

"I slept like a log"

after taking **NEW**

NOW in any language, NOLUDAR 300 is synonymous with sound, restful sleep.

- EFFECTIVE: New NOLUDAR 300 acts promptly to induce sound, refreshing sleep of normal duration and quality1,2,3 ... followed by a clear-eyed awakening, without "hangover" effects.
 - SAFE: NOLUDAR 300 is free of barbiturate risks such as addiction or overdosage. Even minor side reactions are rare.1,2,4 In terms of safety, NOLUDAR "appears to afford all one can possibly expect from a drug of this type."1
- HIGHLY In a study of 1015 cases,1 "all patients expressed CEPTABLE: satisfaction with the quality of action" of NOLUDAR. "... 97.9 per cent rated the hypnotic effect of NOLUDAR as at least equal, or superior to barbiturates they had previously received."
- INDICATIONS: Insomnia due to mental unrest, excitement, fear, worry, apprehension or extreme fatigue.
 - DOSAGE: Adults-One 300-mg capsule before retiring. Do not exceed prescribed dosage.
- REFERENCES: 1. O. Brandman, J. Coniaris and H. E. Keller, J.M. Soc. New Jersey, 52:246, 1955. L. J. Cass, W. S. Frederik and J. B. Andosca, New England J. Med., 253:586, 1955. 3. E. H. Loughlin, W. G. Millin, J. Schwimmer and M. Schwimmer, Internal. Rec. Med., 168: 52, 1955.
 4. P. A. Radnay, Postgrad. Med., 21:617, 1957.

 NOLUDAR®—brand of methyprylon

ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc · Nutley 10 · New Jersey

OLUDAF

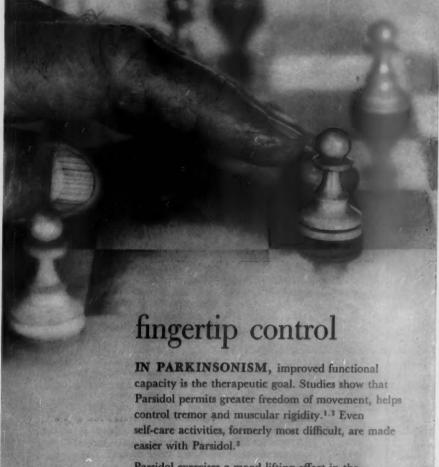
DISAPPOINTED with skeletal muscle relaxants that cause GI distress, drowsiness, and

dizziness....





ARMOUR PHARMACEUTICAL COMPANY . KANKAKEE, ILLINOIS / a leader in biochemical research



Parsidol exercises a mood-lifting effect in the

patient at the same time that his physical coordination and dexterity return. Though effective by itself, Parsidol is also compatible with most other anti-parkinsonian drugs. Side effects are minimal. Most patients respond to a maintenance dosage of 50 mg. q.i.d.

7. Doshay, L. J. et al. J.A.M.A. 160:348 (Feb.) 1956. 2. Berris, H.: T. Lancet 74:245 (July) 1954.

PARSIDO

brand of ethopropazine hydrochleride



CLINICAL NOTES

HEMATOLOGY.

A NEW INTRAVENOUS IRON COMPLEX

ASTRAFER® (ASTRA) I.V.

COMPOSITION A soluble, high-molecular, iron carbohydrate complex, equivalent to 20 mg. trivalent iron per cc., not to be confused with saccharated iron complexes.

PROPERTIES

ASTRAFER[®]I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

INDICATIONS Severe iron deficiency anemia characteristic of
late pregnancy and massive or repeated blood loss,
where rapid replenishment of large iron deficits is
mandatory, and wherever orally administered iron
may be either ineffective or poorly tolerated. To
date, there is no evidence that this agent is of any
value in anemias of polyarthritis or chronic nephritis.
CONTRAINDICATIONS are pernicious anemia, leukemia or
bone marrow depression, and liver damage.

DOSAGE Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature * accompanying each package.

SUPPLIED 5 cc. color-break ampules, boxes of 10

ASTRAFER® (ASTRA) I. V.

*Further information including clinical background and detailed dosage instructions available to physicians on request.

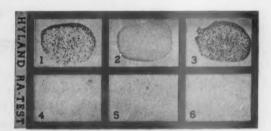
ANTRA PHARMACEUTICAL PRODUCTS, INC. Worcester, Mass. U.S.A.



NEW...HYLAND RA-TEST A FAST, SIMPLE, RELIABLE SCREENING TEST FOR RHEUMATOID ARTHRITIS

a rapid slide modification of the latex fixation test

RA-TEST



EASY TO PERFORM—just mix separate drops of Latex-Globulin Reagent with: (1) patient's diluted serum, (2) Negative Control Serum, and (3) Positive Control Serum on divided areas of slide.

EASY TO READ—positive reactions (indicating presence of rheumatoid factor) are clearly visible to the naked eye in a few seconds. Negative tests remain smooth, with no visible clumping.

SUPPLIED—in compact kits containing 5 cc. Latex-Globulin Reagent, 2 cc. Positive Control Serum, 2 cc. Negative Control Serum, 100 cc. Glycine-Saline Buffer Diluent, and divided glass slide. Each kit sufficient for at least 100 tests. Test components are also available separately.

HYLAND LABORATORIES

Los Angeles 39, California · Yonkers, New York

HYLAND



*Trade Mark of Hyland Laboratories

specific for situational stress

PHENERGAN aids in carrying your patients through difficult periods of stress. It creates a state of quiescence without depressing vital functions. Because of its many actions and uses, PHENERGAN is used extensively in obstetrics, surgery, and in wide-ranging areas of medicine.

versatile in action

Psychic sedative

Antiemetic

Antihistaminic

Analgesic and narcotic potentiator

indications:

Nausea and vomiting

Motion sickness

Surgical sedation

Obstetrical sedation

Oral surgery and dental

procedures

Allergic reactions

PHENERGAN°

HYDROCHLORIDE

Promethazine Hydrochloride, Wyeth

INJECTION . TABLETS . SYRUP . SUPPOSITORIES

Comprehensive literature supplied on request

Motion sickness Nausea and vomiting Surgical and

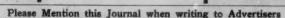
obstetrical sedation





Allergic reactions







Please Mention this Journal when writing to Advertisers

relieve the tension



-and control its G.I. sequelae



Patient A.S., age 53.
Intermittent crises of severe pain over 2 year period;
hospital management with Sippy regimen provided relief of
symptoms; however, symptoms recurred after each sojourn.



PATHIBAMATE (Tabs. †t.i.d. and H.S.); prompt relief of symptoms. Radiograph (21 days later) confirms healing of minute lesser curvature gastric ulcer crater.

predictable results in the control

of tension and G.I. trauma

Pathibamate^{*}

v in anticipation of periods of emotional stress, or therapeuti-

Used prophylactically in anticipation of periods of emotional stress, or therapeutically to relieve tension and curb hypermotility and hypersecretion, Pathibamate is particularly well-formulated for the control of gastrointestinal disorders.

Pathebamate combines Meprobamate (400 mg.)—the noted tranquilizer-muscle relaxant widely accepted for management of tension and anxiety states—and Pathelon (25 mg.)—an extremely well-tolerated anticholinergic, long noted for prompt symptomatic relief based on peripheral atropine-like action with few side effects.

Indications

Duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, gastric hypermotility.

Supplied:

Bottles of 100 and 1,000. Each tablet (yellow, 1/4 -scored) contains Meprobamate, 400 mg., PATHILOW Tridinexethyl Chloride, 25 mg.

Administration and Dosage:

1 tablet three times a day at mealtimes and 2 tablets at bedtime. Adjust dosage to patient response. Contraindicated in glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Also Available: Pathilon in four forms - Tablets of 25 mg., plain (pink) or with phenobarbital, 15 mg. (blue);

Parenteral - 10 mg./cc. - 1 cc. ampuls;

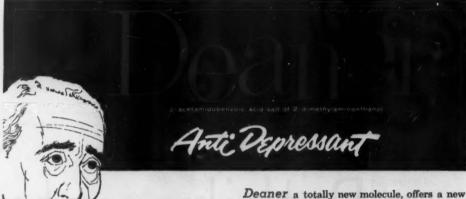
Pediatric Drops - 5 mg./cc. - dropper vials of 15 cc.

*PATHILON is now offered as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could interfere with the results of certain thyroid function tests.



LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

In Mild Depression



Do Not confuse it with tranquilizers

'Deaner' must not be confused with tranquilizing or sedative drugs which may aggravate depression. On the contrary, 'Deaner' is often used to counteract druginduced depression.

'Deaner' is valuable as an emotional normalizer in many situations other than depression, such as behavior problems with agitation. Nor should 'Deaner' be considered an ordinary stimulant. Its gentle action differs from that of other stimulants in that it leads to increased useful energy and alertness without the undesirable side effects of the amphetamine-like drugs.

type of alleviation in depression, fatigue states and many other emotional disturbances. Its physiologic effectiveness as a safe central nervous system stimulant is attributed to its activity as a probable precursor to acetyl-

Deaner leads to better ability to concentrate, increased daytime energy, sounder sleep (with less sleep needed), and a more affable mood.

Deaner acts gently, gradually, and its effects are prolonged...without causing hyperirritability...without loss of appetite...without elevating blood pressure or heart rate... without sudden letdown on discontinuance.

Deaner is valuable in the treatment of children, especially those whose performance is impaired by behavior problems, whose attention span is too short, and who are emotionally unstable, unpredictable, and unadaptable.

Dosage: Initially, 1 tablet (25 mg.) in the morning. Maintenance dose, 1 to 3 tablets; for children, 1/4 to 3 tablets. Three to four weeks of therapy may be required for maximum benefit.

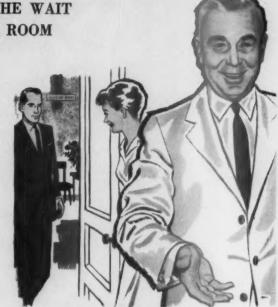
Literature and bibliography available upon request.



SUSAN'S IDEA TOOK THE WAIT OUT OF THE WAITING ROOM

She kept complaining about my old x-ray machine—said she could accomplish more if only she had that new G-E unit I'd talked about. She'd have fewer retakes too—most of them were caused by the long exposures necessary with low power.

From the day my new Patrician combination arrived I'm sure Susan felt her persistence had turned the trick. (And you know — she is working faster today!)



Patrician speeds x-ray examinations

... and for such modest cost



Progress is Our Most Important Product
GENERAL ELECTRIC

You'll find your work load lighter with Patrician's big-table convenience. Best news is 200-ma, 100-kvp power, electronically timed. Self-tending recipromatic Bucky. Finger-tip control of fluoroscopic screen or optional spot-film device. Angulation to 15° Trendelenburg. Automatic Bucky-slot closures for x-ray safety. Ask your G-E x-ray representative for full details. Or clip coupon for a copy of

| | Patrician |
|-----|--|
| GEN | AY DEPARTMENT HERAL ELECTRIC CO. HOUSe 1, Wisconsin, Rm. M-31 |
| 0 | Piease send me your 16-page PATRICIAN bulletin Facts about deferred payment MAXISERVICE ® rental |

our fully illustrated catalog.

| | ☐ Facts about deferred payment ☐ MAXISERVICE ® rental | | | | | | | | | | | | |
|---------|---|--|----|--|--|--|--|------|------|--|--|-----|--|
| Name . | | | | | | | | | | | | * * | |
| Address | | | ** | | | | | | | | | | |

inflammatorysuppressivé inflammatorycorrective antiallergic antirheumatic

new, exclusive



Prednis-CVP

dual anti-inflammatory

Inflammatory-suppressive ... potent, prompt, sustained action with prednisolone

inflammatory-corrective ... reduction of abnormal capillary permeability with citrus bioflavonoids

"built-in" protection

with citrus bioflavonoids... against ecchymoses, purpuras, gastric hemorrhage and other steroid-induced capillary damage

with antacids ...
against gastric distress,
digestive upsets, nausea



in rheumatoid arthritis bronchial asthma eczemas

and other inflammatory, allergic and rheumatic conditions

suggested dosage:

Average initial dose, 2 to 5 capsules daily, in divided doses; in severe cases, 6 to 10 capsules daily. Gradually reduce dosage to effective maintenance level.

Bottles of 30, 100 a 500 capsules.

Samples and literature from

Each PREDNIS-C.V.P. capsule provides:

| PREDNISOLONE | 4 mg. |
|------------------------------|---------|
| CITRUS BIOFLAVONOID COMPOUND | 100 mg. |
| ASCORBIC ACID (C) | 100 mg. |
| ALUMINUM HYDROXIDE | 100 mg. |
| MAGNESIUM OXIDE | 100 mg. |

arlington-funk laboratories

division of U. S. VITAMIN CORPORATION . 250 East 43rd Street . New York 17, N. Y.



. . . TRUE ECG PORTABILITY



. . VECTORCARDIOGRAPHY



. . PHONOCARDIOGRAM



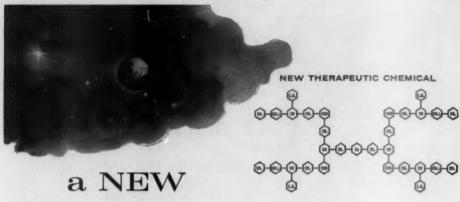
.. HEART SOUND

ou take it for granted that today's medical instrumentation is basically accurate and reliable. But beyond these expected fundamentals, the dependability usefulness - and convenience of any instrument depends almost wholly on how much the instrument manufacturer knows of your needs and how well he has applied this knowledge. For more than 40 years, Sanborn Company has asked the general practitioner and medical school teacher . . . the cardiologist and researcher . . . the industrial physician and clinician, what they particularly need for greatest usefulness and value in diagnostic and research instrumentation. The instruments shown here are typical Sanborn answers to these needs . . . exemplified in the field of cardiography by the Model 300 Visette - the first ECG to make "18-pound portability" a practical reality. Since its introduction less than two years ago, the Visette has literally become the "travelling diagnostic companion" of over 4000 of your colleagues.

When you choose any instrument to provide you with information for diagnosis and research, consider the instrument's background and past — as a good gauge of its future value to you. Sanborn Company, Medical Division, 175 Wyman Street, Waltham 54, Massachusetts.

SANBORN COMPANY

Visit us at Booths 45-46 at American College of Physicians



DIMENSION IN THE

TREATMENT OF CONSTIPATION

DOXIDAN

The Surfactant Laxative

"Ideal" laxative therapy has now been made possible by the application of a new principle based on the double surfactancy of the new therapeutic chemical, calcium bis-(dioctyl sulfosuccinate).

Doxidan provides positive, reliable laxative action with:

- Greatly reduced laxative dosage and optimal surfactancy.
- The least possible disturbance of normal body physiology.
- Freedom from the discomfort of bowel distention.
- Freedom from "oily leakage" and interference with vitamin absorption.
- Freedom from pain and "cramping."
- Greatly reduced risk of laxative habituation.

No longer is a "cathartic flush" needed to expel a hardened resistant fecal mass. Instead, once calcium bis-(dioctyl sulfosuccinate) has rendered the mass malleable and mobile, a gentle peristaltic stimulant is all that is needed to correct bowel dysfunction.

Doxidan is a true synergistic combination of calcium bis-(dioctyl sulfosuccinate), the new surfactant fecal softener, and Danthron, a mild peristaltic stimulant which acts solely in the lower bowel.

This new dimension in treatment (Doxidan therapy) results in soft, "normal" stools gently stimulated to evacuation.

Each maroon soft gelatin capsule contains 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate).

dosage: For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Give at bedtime for 2 or 3 days or until bowel movements are normal.

supplied: Bottles of 30 and 100 soft gelatin capsules.

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO



"flavor-timed" dual-action coronary vasodilator

Dilcoro

for ANGINA PECTORIS

ORAL (tablet swallowed whole) for dependable prophylaxis

SUBLINGUAL-ORAL

for immediate and sustained relief

-0.4 mg. (1/150 grain) - acts quickly

itrus "flavor-timor"

staerythritel intranitrate

-15 mg. (1/4 grain)-prolongs action

For continuing prophylaxis patients may swallow the entire Dilcoron tablet.

Bottles of 100.

rage prophylectic deser 1 tablet four times daily (before meals and at bedtime).

Therepostic dees:

1 tablet held under the tongue until citrus
flavor disappears, then swallowed.

Through his monumental work on conditioned reflexes, and his sham-feeding experiments on dogs,

Ivan P. Paylo

(1849-1936) established the relationship between central nervous system and stomach, showed that increased flow of gastric juice eventuates from vagal stimulation.

Milpath Miltown + anticholinergie

suppresses vagal stimulation, provides relief of pain, spasm, anxiety and tension without belladonna or barbiturates.

Side effects are minimal.

IVAN P. PAVLOV

Formula: Each scored tablet contains: meprobamate 400 mg., tridihexethyl chloride 25 mg.

Dosage: 1 tablet t.i.d. with meals and 2 tablets at bedtime,

Indications: duodenal and gastric ulcer • colitis
spastic and irritable colon • gastric hypermotility • gastrities ophageal spasm • intestinal colic • functional diarrhea • G. I. symptoms of anxiety states.

Literature and samples on request.



W WALLACE LABORATORIES

New Brunswick, N. J.



ELECTIVE AND TRAUMATIC

use XYLOCAINE first...
as a local anesthetic
or a topical anesthetic



Xylocaine HCl solution, the versatile anesthetic for general office surgery, relieves pain promptly and effectively with adequate duration of anesthesia. It is safe and predictable. Local tissue reactions and systemic side effects are rare. Supplied in 20 cc. and 50 cc. vials; 0.5%, 1% and 2% without epinephrine and with epinephrine 1:100,000; also in 2 cc. ampules; 2% without epinephrine and with epinephrine 1:100,000.

XYLOCAINE® HCI SOLUTION



Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.



44.4. PAT. NO. 2.441.489 MADE IN U.S.A.

REACHING FOR THOSE 9B's NEARLY PUT ME ON THE SHELF...

Reaching for 9B shoes and other top shelf sizes is no joke... it gave me a terrible kink in my back.



Percodan-Demi & Percodan Tablets

FOR PAIN

ACTS FASTER—usually within 5-15 minutes. LASTS LONGER—usually 6 hours or more, MORE THOROUGH RELIEF—permits uninterrupted sleep through the night. RARELY CONSTIPATES—excellent for chronic or bedridden patients. VERSATILE—new "demil" strength permits dosage flexibility to meet each patient's specific needs. Percodan Demi provides the Percodan formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit forming. Federal law permits oral prescription.

Each Percoom. Tablet contains 4,50 mg. dihydrohydroxycodeinone nydrochloride, 0,78 mg. dihydrohydroxycodeinone terephthalate, 0,38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

AND THE PAIN WENT AWAY FAST



Literature? Write ENDO LABORATORIES







The pain went away fast — in just 15 minutes — and I was back on the job the next morning! But mot one 9B customer came in the whole day!



RAUTRAX



RAUDIXIN plus an entirely new diuretic



a natural companion to famous RAUDIXIN to help solve the problem –

HYPERTENSION

SQUIBB



apprint an energy are shots flatfiells.

in skin disorders



DEXAMETHASONE

treats more patients more effectively

- a new order of magnitude in corticosteroid effectiveness
- a new order of magnitude in margin of safety

Striking clinical results with DECADRON are reported in 92 percent of 319 patients with dermatological disorders, including cases previously unresponsive or resistant to corticosteroids. There were no major complications, and even minor side effects occurred in less than eight percent of patients.

Moreover, in many cases reactions induced by previous steroid therapy, such as edema, Cushingoid appearance, headache, vertigo, muscular weakness, depression, hirsutism, and glycosuria, disappeared during therapy with DECADRON. †Analysis of clinical reports.

Desage: One 0.75 mg, tablet of DECADRON will usually replace one 4 mg, tablet of methylprednistor triamcinolone, one 5 mg, tablet of prednisone or prednisolone, one 20 mg, tablet of hydrocortisone, or one 25 mg. tablet of cortisone

Supplied: As 0.75 mg, and 0.5 mg, scored, pentagon shaped tablets in bettles of 100 and 100 @1958 Merck & Co., Inc. *DECADRON is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

ANNALS OF INTERNAL MEDICINE

VOLUME 50

MARCH, 1959

NUMBER 3

EFFECT OF THE CARDIAC ARRHYTHMIAS ON THE CORONARY CIRCULATION * †

By ELIOT CORDAY, M.D., F.A.C.P., HERBERT GOLD, M.D., Los Angeles, California, LAURO B. DE VERA, M.D., Manila, P. I., JOHN H. WILLIAMS, M.D., Edmonton, Alberta, and Joshua FIELDS, M.D., Los Angeles, California

This study will consider the hemodynamic disturbances of the coronary flow which occur during cardiac arrhythmias. It has been shown that fast cardiac arrhythmias can precipitate severe disturbances of the systemic circulation leading to coronary insufficiency, 1-5 cerebral vascular insufficiency, 6 and renal 7 and hepatic necrosis.8 There have been numerous reports 4,5 of patients with abnormal cardiac rhythms complaining of precordial pain and manifesting electrocardiographic changes of myocardial ischemia which may persist for hours after the subsidence of the arrhythmia. When death occurs in these patients with manifestations of coronary insufficiency, postmortem studies often show myocardial damage, such as subendocardial necrosis and fibrosis.

As a result of previous experimental studies, 9-11 it has been concluded that coronary artery flow is maintained or increased during tachycardias. However, it now seems that this conclusion is open to question for several reasons. In the experiments referred to, 9-11 electrical stimulation was used to produce the arrhythmias, which were recorded at a slow recording speed. Reëxamination of some of these published tracings discloses a significant reduction in "average" coronary flow. Furthermore, it is not certain that

^{*} Received for publication October 31, 1958.

Presented at the Thirty-ninth Annual Session of The American College of Physicians,

Atlantic City, New Jersey, April 28, 1958.

From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, and the Department of Medicine, University of California School of Medicine, Los Angeles.

† This study was aided by financial grants of the Beneficial Life Insurance Co. and Charles P. Skouras Foundation.

Requests for reprints should be addressed to Eliot Corday, M.D., 436 North Roxbury Drive, Beverly Hills, California.

tachycardias were actually produced in every instance by the electrical stimulation. Our experience has indicated that when the heart is stimulated at rapid rates it does not necessarily respond to each stimulus. In over one-half of our experiments, the myocardium when stimulated electrically either failed to respond to the stimulus, or A-V block or mechanical alternans occurred. In such instances, the ventricular rate is only a fraction of the rate of stimulation and could not be considered to be tachycardia. Careful analysis of the electrocardiogram and blood pressure recordings must be made with rapid recorders to ensure that the ventricle is responding both electrically and mechanically to the stimuli, otherwise one cannot be sure that the desired arrhythmia is actually present.

Because of these possible sources of error, and because the conclusions previously reported do not seem to correspond to the clinical observation of coronary insufficiency during tachycardia, it was decided to reinvestigate the effect of the arrhythmias on the coronary circulation. Several methods of producing the arrhythmias and four separate technics were used for evaluating the coronary flow. It is hoped that the new hemodynamic principles learned in this study will give the clinician a better understanding of the behavior of the coronary circulation during the arrhythmias, and a new physiologic approach to treatment.

PROCEDURE

To determine the effect of various arrhythmias on coronary artery flow, control measurements were first made in cannulated coronary arteries of 246 dogs and four pigs. The methods used for measurement of the coronary flow have been described elsewhere.^{13, 14} These include the use of the rotameter, the photoelectric dropmeter and the open-drop method. The coronary artery flow is measured by the first two methods with an intact peripheral coronary resistance. The collateral circulation (retrograde) and forward directed (antegrade) flows are compared, using the open-drop method without influence of peripheral coronary resistance. Only antegrade coronary flow was determined in the pig, because the collateral flow was too minute to measure. In some experiments the coronary sinus flow was measured simultaneously with the coronary artery flow. A photoelectric dropmeter was used for recording both in a closed circuit, with apparently an intact peripheral resistance.

Coronary flow was then measured during various arrhythmias, occurring spontaneously, or produced by either mechanical stroking or the application of aconitine to the heart. In addition to the flow measurements, the coronary artery and systemic blood pressures were often recorded by attaching the coronary catheters to Statham strain gauges. The central venous pressure and cardiac output were often recorded. On many occasions the arrhythmia reverted to normal sinus rhythm during the course of the experiment. Because it has been demonstrated by Blumgart 15 that the col-

lateral circulation increases anatomically following coronary ligation, these experiments were repeated in 12 dogs four weeks following such ligation. The illustrations presented in this study (figures 1, 2, 4–7) are from dogs with chronically ligated arteries that have resulted in collateral circulations with higher flow and pressure than those observed in normal coronary arteries.

The results will clearly show that the coronary sinus flow behaves in a somewhat different fashion than does the coronary artery flow. Therefore, an experimental interpretation must consider method and site of measurement. The coronary sinus flow demonstrated a lesser degree of change than did the coronary arterial circulation, due to unknown mechanisms which increase myocardial blood flow. Brachial artery tracings were also recorded in patients during naturally occurring premature auricular and ventricular systoles, auricular flutter, tachycardia and fibrillation, to determine their effect on systemic blood pressure and to compare the results found in the experimental animal.

RESULTS

The various arrhythmias experimentally induced were: premature auricular systoles, premature ventricular systoles, auricular tachycardia, auricular flutter, auricular fibrillation, ventricular tachycardia and ventricular fibrillation. When aconitine-induced arrhythmias were obtained, the rhythm could often be converted to regular sinus rhythm by cooling the aconitine focus with ice or an ethyl chloride spray or intravenous glycosides.

Premature Auricular Systoles: Frequent premature auricular systoles occurring as in bigeminy or in short runs, were often found to have a marked effect on the coronary flow as measured by the open-drop and dropmeter methods of measuring coronary artery and sinus flow over a period of 30 seconds. In 70 dogs a significant reduction of both the antegrade (forward) and retrograde (collateral) coronary flow occurred during this arrhythmia. In 12 instances the coronary artery flow rose slightly when premature auricular systoles were produced by mechanical stroking of the atrium. The average reduction in the coronary artery flow due to premature auricular systoles using the open-drop method was: antegrade flow, 9.5%; retrograde flow, 10.1%. The range was from plus 10 to minus 34%.

Premature auricular systoles also usually caused a marked reduction in the systolic and diastolic systemic blood pressures. Often there was a slight increase in the blood pressure of the following sinus beat (figure 1). In some experiments the antegrade (forward) and retrograde (collateral) coronary blood pressures were recorded simultaneously with the systemic blood pressure (figure 1). Both the systolic and the diastolic coronary blood pressures were found to drop considerably during premature auricular beats. Often there was no pulsation, or a diminished pulse pressure, in both segments of the coronary artery.

The rotameter, because of its lag, could not faithfully record the changes in coronary flow during the premature systoles.

The photoelectric dropmeter revealed an average decrease in coronary artery flow during auricular premature systoles of 5%. Comparable results were noted in coronary sinus flow. Occasionally, premature auricular systoles increased the coronary flow slightly because of a transient increase of cardiac rate.

Premature Ventricular Systoles: Frequent premature ventricular systoles occurring spontaneously, or produced by gentle stroking of the ventricle with an applicator, usually caused a reduction in the coronary artery blood flow. With the use of the open-drop method, the average reduction in 76

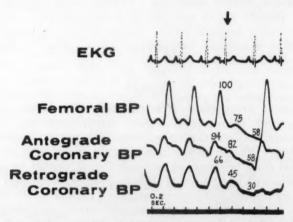


Fig. 1. Simultaneous recordings of the electrocardiogram, femoral blood pressure, and antegrade and retrograde coronary blood pressure which demonstrate a marked drop in the systolic and diastolic blood pressure following a premature auricular systole. Figures 1, 2, 4-7 were recorded on a dog four weeks subsequent to ligation of the anterior descending coronary artery, and thus retrograde pressure is almost as high as antegrade pressure.

animals was found to be: antegrade flow, 14.6%; retrograde flow, 12.4%. With the use of the photoelectric dropmeter, the average reduction in arterial flow was 12%. Coronary sinus flow dropped an average of 10.6%. In some instances, frequent premature ventricular systoles caused a reduction of as much as 25% in the coronary artery flow. When frequent premature ventricular systoles occurred in groups of three or four, the systemic blood pressure would often drop to shock levels and take up to a minute to recover. As described by Katz, 16 the first post-extrasystolic beat would usually result in a higher systolic pressure than normal.

The systemic blood pressure and the antegrade and retrograde coronary blood pressures were all found to be markedly depressed by premature ventricular beats (figure 2). A single premature ventricular beat could result in a marked drop in the aortic diastolic blood pressure, and the systolic

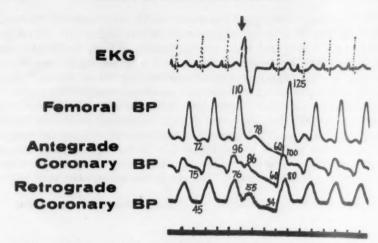


Fig. 2. Tracing demonstrates the effect of a premature ventricular systole on the systemic and antegrade and retrograde coronary blood pressures. Note that there is a small systolic pulsation and subsequently a marked drop in the diastolic blood pressure immediately following the premature ventricular systole.

pulse wave also was usually altered in form and greatly diminished. If the premature ventricular systole occurred so early that the heart had no time to fill, the systolic pulsation in the coronary artery was usually absent and the diastolic coronary pressure was lowered.

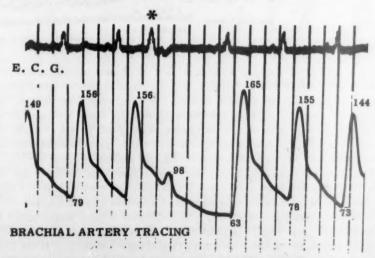


Fig. 3. Simultaneous electrocardiographic and brachial artery tracings of a patient demonstrating the effect of a premature ventricular systole. Note the marked drop in diastolic pressure caused by the premature systole. The T waves of the electrocardiogram show ischemic changes immediately after the premature beat.

Brachial artery tracings of premature ventricular systoles in the human were similar to those of the experimental animal (figure 3). These premature beats resulted in a small systolic ejection of blood and a precipitous drop in the diastolic pressure. In one patient who had angina pectoris with premature systoles (figure 3), we confirmed the observation that the T waves become inverted following a premature systolic contraction.^{1, 2, 17}

Paroxysmal Auricular Tachycardia: With the onset of auricular tachycardia, the systemic blood pressure of both the human patient and the experimental animal usually dropped. In many instances, when the rate was very rapid it fell to shock levels (figure 4). In the dog, the faster the rate, the greater was the drop in the systemic and coronary artery blood pressures and the coronary artery flow. The central venous pressure rose and the

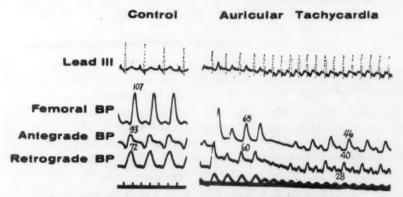


Fig. 4. Tracing demonstrates the marked drop in femoral and coronary blood pressures subsequent to the induction of a paroxysm of auricular tachycardia.

cardiac output often dropped 30% to 65%. With slowing of the rate, the coronary artery flow and pressure, systemic pressures, venous pressure and cardiac output returned toward normal. By the open-drop technic, the average decrease in the antegrade coronary flow in rapid auricular tachycardia was 34.7%, and in the retrograde circulation, 35.3%. Thus, the forward and collateral flows were similarly affected. The rotameter method demonstrated an average reduction of 38.2% and the dropmeter 35.7%.

The average reduction in coronary sinus flow was 24%. Coronary sinus flow did not bear a constant relationship to coronary artery flow. The coronary sinus flow showed constant fluctuation (figure 8), and sometimes increased temporarily as much as 34% over control levels, while the coronary artery flow was 14% reduced. It often dropped as much as 36%, while the simultaneous coronary artery flow diminished 60%. If the blood pressure fell to shock levels, the coronary sinus flow remained at reduced levels. When the arrhythmia suddenly converted to regular sinus rhythm, the coronary sinus flow often increased 200% above the control flow for a

20-second interval and then returned to previous control values. The coronary artery flow did not demonstrate the same degree of rebound phenomena on termination of tachycardia.

Auricular Fibrillation: When auricular fibrillation with rapid ventricular rate was produced, the systemic blood pressure invariably dropped and the pressure in the proximal and distal coronary artery segments also fell (figure 5). Although the systolic pressure occasionally spiked to near normal, the diastolic pressure decreased considerably (figure 5). The average reduction in the antegrade coronary flow was 32.9%, and in the retrograde flow, 39.8%. Comparable reductions in coronary artery flow—40.3% using the rotameter and 44.4% with the dropmeter—were observed. The faster the ventricular rate, the lower were the systemic blood

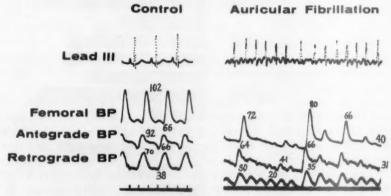


Fig. 5. Tracing demonstrates a marked drop in systemic and coronary blood pressures subsequent to the induction of auricular fibrillation.

pressure and the coronary artery flow. As the rate slowed, the blood pressure returned toward normal, as did the coronary artery flows. However, in many experiments where auricular fibrillation lasted for hours, the coronary artery flow remained very much reduced, as did the systemic, antegrade and retrograde coronary blood pressures. When the rhythm could be converted to regular sinus rhythm, the systemic and coronary pressures and coronary artery flows returned to control levels.

The average reduction in coronary sinus flow was 27%. The coronary sinus flow constantly changed. At times the blood flow was double the control level, but within a few seconds was decreased as much as 30% with the same ventricular rate. Simultaneous recording of the flow in the anterior descending coronary artery usually showed a marked drop during the rapid tachycardias, and thus did not always correspond to the coronary sinus flow. The coronary sinus flow showed most marked increases when the blood pressure rose momentarily after a period of hypotension. This

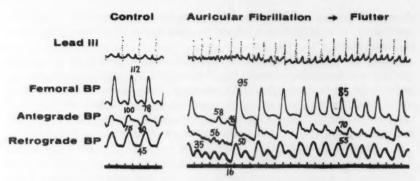


Fig. 6. Tracing demonstrates changes in systemic and coronary blood pressures when the cardiac rhythm is converted from auricular fibrillation to auricular flutter.

transient increase in flow was of short duration, often lasting only 10 seconds before decreasing again.

The systemic blood pressure tracings of the human were similar to those of the experimental animal. The faster the rate, the greater was the drop in blood pressure.

Auricular Flutter: When auricular flutter with rapid ventricular rate occurred, the systemic blood pressure and coronary artery blood pressures decreased considerably. However, if the ventricular rate was slowed because of 2:1 or 3:1 heart block, the pressures and coronary artery flows increased toward normal. When auricular fibrillation converted to auricular flutter, with a slower and more regular ventricular rate (figure 6), the pressure and coronary flow increased considerably. During auricular flutter, the average decrease by the open-drop method in antegrade directed coronary flow was 22.9%, and in retrograde flow, 18%. The range was

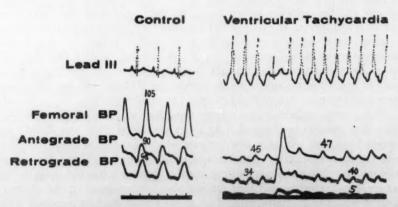


Fig. 7. Recordings demonstrate the effect of ventricular tachycardia upon the systemic and coronary circulation.

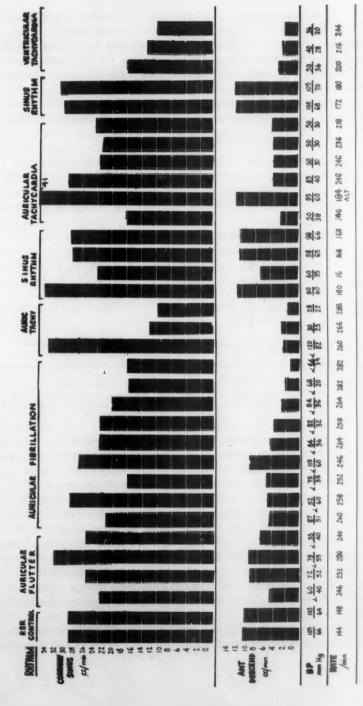


Fig. 8. Graphs demonstrate the effect of various cardiac arrhythmias on simultaneously recorded coronary sinus and anterior descending coronary artery blood flows. The arrhythmias were produced by applying aconitine to either the atrium or the ventricle. These 34 observations were recorded over a period of three hours. Mechanical alternans (alt) occurred only occasionally.

7% to 56%. The average flow, using the rotameter, showed a comparable decrease of 22.7%; with the dropmeter, the reduction was 20.2%.

Measurements of coronary sinus flow again showed fluctuations which did not correspond to the more consistent decrease in coronary artery flow. The coronary sinus flow occasionally showed an increase of up to 15%, but more commonly a drop of 20%.

In the human, the brachial artery tracings were similar to the curves of coronary pressure in the experimental animal. If the ventricular rate was slow, the pressure curves were little affected by auricular flutter.

Ventricular Tachycardia: When ventricular tachycardia occurred spontaneously, or was produced by stroking the heart, or by the application of aconitine, the systemic blood pressure and the antegrade and retrograde coronary pressures dropped precipitously (figure 7). The coronary artery flows were found to be markedly reduced. The average antegrade flow was

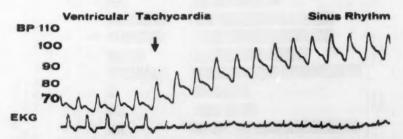


Fig. 9. Recordings demonstrate the marked hypotension which occurs during ventricular tachycardia. When the rhythm spontaneously converts to sinus rhythm, the systemic blood pressure returns toward normal. Note that the rate of the ventricular tachycardia was almost the same as that of the succeeding sinus rate. However, measurements of the systemic blood pressure and coronary flow were markedly reduced during the paroxysm of ventricular tachycardia.

reduced by 52.5%, the retrograde by 58.9%. The decrease in flow ranged from 14% to 90%. The rotameter demonstrated an average drop in coronary artery flow of 48.2% during this arrhythmia. The rate of the ventricular tachycardia per se did not seem to be the only factor in the reduction of the blood pressure and the coronary artery flow. In figure 9 the rate of the ventricular tachycardia was the same as the succeeding sinus rate. However, there was a great reduction in the coronary artery flow and blood pressure during ventricular tachycardia. When the ectopic focus was near the apex of the ventricle, the coronary flow and systemic pressure were less affected than when it originated at the base of the ventricle.¹⁸

Coronary sinus flow diminished an average of 50% during a paroxysm of ventricular tachycardia, while the coronary artery flow simultaneously decreased 66% (figure 8).

Ventricular Fibrillation: With the onset of ventricular fibrillation, the systemic and the antegrade and retrograde coronary pressures all dropped

to exceedingly low levels, and the coronary flow became so scant that it could hardly be measured.

Summary of Experimental Results: Thus, each of the arrhythmias studied resulted in a significant reduction in coronary artery flow if it was irregular or rapid (above 190 per minute). These arrhythmias also cause distinct reduction in coronary and systemic blood pressure. Coronary sinus flow, however, showed great fluctuations. When marked hypotension persisted, it diminished. The clinical aspects of these findings will now be discussed.

DISCUSSION

Clinical Correlation of Experimental Studies: Kory and Meneely ¹⁰ demonstrated in patients that when auricular fibrillation was converted to normal sinus rhythm, the average cardiac output increased by 43%. Smith et al. ²⁰ demonstrated in humans that the cardiac output increased one fourth or more when the rhythm became normal after auricular fibrillation. Harvey and her group ²¹ showed that the cardiac output in five patients with auricular flutter increased when the arrhythmia was abolished. The blood pressure also rose after conversion. The average increase in cardiac output in these five cases was 38.8%. In the present experimental investigation it was found that fast arrhythmias caused a reduction in the cardiac output of 20% to 67%.

Experimentally, premature auricular and ventricular systoles often cause a reduction in the systemic and coronary blood pressure and in the coronary sinus and arterial flows. This drop in pressure has been demonstrated in the human by Katz ¹⁶ and Eliakim and Braun.²² We have also obtained tracings in the human which demonstrate a marked drop in the diastolic and systolic blood pressures in many of these arrhythmias. It is true that a compensatory increase in the systemic blood pressure occurs following a premature ventricular beat and tends to counteract or offset the preceding drop in the systemic blood pressure. However, as the coronary filling occurs principally in diastole, it is believed that this compensatory increase in systolic pressure does not adequately compensate for the previous drop in the diastolic pressure.

Wolff demonstrated that severe hypotension occurred in 56% of patients with tachycardia with ventricular rates above 180 per minute.³⁷ This is probably because of an inadequate filling of the heart due to shortened diastole. It has been found in this laboratory that in normal sinus rhythm a reduction in aortic blood pressure is accompanied by a corresponding reduction in coronary sinus and artery flow (figure 10). When the systemic blood pressure is restored toward normal, both the coronary sinus and the coronary artery flow and coronary blood pressures also increase toward normal in a linear fashion.¹⁴ In other words, coronary artery as well as coronary sinus flow was found to be dependent upon the systemic

blood pressure. A rise in blood pressure of 20 mm. of Hg could result in a 30% increase in coronary artery and sinus flow (figure 10). This principle also seems to be a major factor in determining the coronary flow during the arrhythmias, since it is demonstrated in the experimentally produced arrhythmias that both the coronary flow and the coronary blood pressure closely correspond to changes in systemic blood pressure.

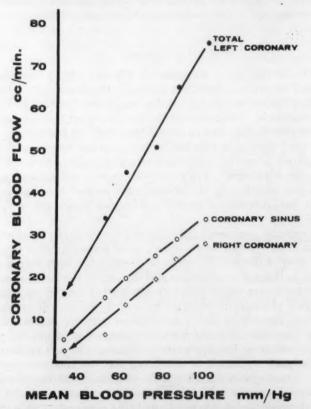


Fig. 10. Graph demonstrates the effect on the coronary circulation of reducing the systemic blood pressure.

Auricular fibrillation with rapid ventricular rate and auricular tachycardia was found to cause a marked reduction in the coronary artery flow, in some instances as much as 60%, depending upon the ventricular rate. The average reduction was about 35%. Auricular flutter, on the other hand, where a 2:1 or a 3:1 block frequently occurred, did not produce such a marked drop in the coronary artery flow, because of the slower ventricular rate. As a matter of fact, if the ventricular rate was slow and regular

during auricular flutter, the flow was often normal. It is interesting that Askey ²⁸ noted a greater mortality rate when auricular tachycardia and fibrillation occurred following myocardial infarction than when auricular flutter occurred. Clinically as well as experimentally, it would seem that flutter causes less reduction in coronary flow than do the other two arrhythmias cited. Since the ventricular rate is an important factor in determining coronary artery flow, greater degrees of block at the A-V node in auricular flutter result in greater coronary flow. It is also true in auricular tachycardia and fibrillation that slower ventricular rates are associated with smaller reductions in coronary artery flow.

As observed above, the measurements of coronary sinus flow during most of the arrhythmias showed marked fluctuation. This finding is in pronounced contrast to the almost linear reduction in coronary artery flow which occurred simultaneously (figure 8). It is difficult to understand these variations in coronary sinus flow, especially since the upsurges in coronary sinus blood flow are associated with increases in oxygen saturation of coronary sinus blood. This relation between coronary artery flow and simultaneous coronary sinus flow seems peculiar, but it is nevertheless valid, because the same recording apparatus was employed for measuring both the coronary sinus and the artery flows. It would therefore appear that when coronary sinus flow increases momentarily as the coronary artery flow diminishes, the myocardium must receive oxygenated blood from some unidentified source. It also appears that the sudden increases in myocardial blood supply are arterial in origin. It may be speculated that shunts have occurred, as, for example, an opening up of the thebesian circulation in response to ischemia of the myocardium. Such a phenomenon would be an attempt to compensate for insufficient flow in the arterial circulation during the arrhythmias. Another possible explanation for the differences between coronary arterial and sinus flow in the arrhythmias is that the function of the vasomotor apparatus of the coronary arteries might have been abolished by the retention ligature placed around the coronary artery. This seems unlikely, however, because coronary artery vasodilatation was observed in these preparations when noradrenalin was administered.14

Regardless of the discrepancy between the arterial and coronary sinus flows in the arrhythmias, it appears that the myocardium receives an insufficient blood flow during many of the arrhythmias, particularly if hypotension is present. The total coronary artery flow determined by preparations with a right heart bypass with the heart pump probably would give valuable information. But because such a preparation corrects for a number of disturbances which occur in the arrhythmias, such as a drop in blood pressure and cardiac output and the impaired filling of the heart due to shortened diastole, its results have only limited value for clinical application.

We have demonstrated in animals 24 that the coronary artery flow and systemic blood pressure in sinus tachycardia was usually maximal when

the ventricular rate was around 160 to 180 per minute. When the ventricular rate was faster, the coronary artery flow and the blood pressure gradually diminished, and above 200–220 per minute there was a marked drop in both the systemic blood pressure and the coronary flow. In the patient with coronary artery narrowing, even if the coronary flow was maximal at a ventricular rate of about 160 per minute the coronary blood supply might not be sufficient to supply the nutritional demands of this increased rate. Therefore, relative coronary insufficiency with ischemia of the myocardium would probably occur. With rates above 180 to 200 per minute, the coronary artery flow decreases and causes an absolute coronary insufficiency. Thus, coronary artery flow is dependent upon the ventricular rate as well as upon the aortic (systemic) blood pressure.

It has been demonstrated 26, 26, 27 that ventricular tachycardia is occasionally a benign condition. Some patients can sustain an elevated ventricular rate for several weeks without demonstrating signs of coronary insufficiency or peripheral collapse. In other instances with a similar ventricular rate, the patient may exhibit severe hypotension and syncope, and may die within a short period of time. This has been called malignant ventricular tachycardia. We believe that, other factors being equal, the site of the ectopic ventricular focus determines the degree of hemodynamic disturbance. In the present study 18 it was observed that if the ectopic focus is near the apex, the coronary artery flow and blood pressure may be only slightly reduced with ventricular rates up to 150 per minute. If the focus is near the base of the ventricle, with the same ventricular rate, there is a much greater reduction in coronary artery flow and systemic blood pressure. This occurs apparently because the contraction wave in the ventricle is directed in an unphysiologic and inefficient direction. At very rapid rates, ventricular tachycardia is "malignant," regardless of the site of the origin of the

Frequent premature auricular systoles and premature ventricular systoles were both found to cause a significant reduction in coronary circulation. Most textbooks state that premature systoles usually need not be treated in the patient with coronary artery disease. However, Katz ¹⁶ believes that, because of the significant drop in systemic blood pressure associated with these premature beats, they should be abolished in patients with coronary artery disease. In individuals with normal coronary arteries, it may be that a transient reduction in the coronary flow of 15% has little significance. However, in the patient with coronary artery disease, where every drop of blood is necessary, a 15% reduction of flow might be critical for the nourishment of the myocardium.

The Antiarrhythmic Effect of Pressor Drugs: It is well known that pressor agents will often promptly convert auricular and ventricular arrhythmias to regular sinus rhythm. 28-35 We have also obtained similarly successful results using noradrenalin and other pressor drugs in converting

both auricular and ventricular arrhythmias such as bradycardia, premature systoles, auricular and ventricular tachycardia and heart block in the experimental animal and in the human patient with a myocardial infarction. To understand the mechanism of the antiarrhythmic action of these pressor substances, a series of experiments was carried out in which the arrhythmias were produced with aconitine in dogs. In most instances we were able to restore regular sinus rhythm promptly by raising the systemic blood pressure by an aortic snare, as well as by the use of pressor drugs such as metaraminol, noradrenalin and methoxamine. Therefore, abolition of the arrhythmia appeared to result from a pressor effect per se, whether produced by drugs or other means. If massive doses of vasopressor drugs were required to raise the blood pressure, fatal cardiac arrhythmias often resulted.

To determine whether the antiarrhythmic action was mediated by way of the vagus nerve, as postulated, ³⁵ or by a direct effect upon the myocardium, the vagus nerve was severed. ³⁶ Following this procedure, it was still possible to abolish the arrhythmias by raising the blood pressure. Thus, it would appear that the antiarrhythmic effect is not mediated exclusively through the vagus, although there is no doubt that this nerve does contribute a cardio-inhibitory action.

To localize further the site of action of the antiarrhythmic effect of raising the blood pressure, another series of experiments was carried out in dogs. 36 The heart was completely denervated by cutting all the blood vessels, trachea and other tissues surrounding it. Circulation was then restored by connecting the heart to the cut vessels again with plastic tubes. After this procedure, auricular and ventricular tachycardias were produced by the application of aconitine. Just as in the previous experiments, these arrhythmias were often abolished by elevating the blood pressure with an aortic snare or pressor drugs.

Thus, much of the antiarrhythmic effect of raising the blood pressure is exerted directly upon the myocardium. It may be speculated that this effect takes place by (1) enhancing the coronary flow, thus either improving the nutrition of the myocardium or removing some irritating metabolites, or (2) stimulating an inhibitory center in the myocardium, or (3) acting in some unknown manner upon the myocardium directly.

In addition to the antiarrhythmic effect of pressor agents, it is well known that these drugs may also produce serious ventricular arrhythmias. In a large series of animals, however, we have noted that ventricular arrhythmias do not appear until the blood pressure is raised either by a snare or by a pressor agent to hypertensive levels, usually above 180 mm. of Hg systolic. Thus, pressor agents appear to exert an antiarrhythmic effect below blood pressures of approximately 180 mm. of Hg, and seem to have an arrhythmia-producing effect above this level. Therefore, when these pressor drugs are used clinically, it is necessary to make sure that the blood

pressure is not raised above a critical hypertensive level, where serious arrhythmias may occur.

In some cases with serious arrhythmias where systemic hypotension is a feature, the administration of pressor drugs may be successful in restoring the blood pressure toward normal but may fail to influence the arrhythmia. One such patient under our care developed a ventricular tachycardia following myocardial infarction. With the onset of the arrhythmia, severe hypotension and loss of consciousness occurred. When noradrenalin was administered the blood pressure rose and consciousness returned but the arrhythmia persisted. Whenever the pressor drug was discontinued, hypotension and unconsciousness immediately recurred. Regular sinus rhythm was finally restored nine hours after the intravenous administration of large doses of quinidine and pronestyl.

Cases of this kind point to the necessity of maintaining the blood pressure by pressor drugs even though the arrhythmia may persist and may require specific antiarrhythmic agents for its abolition. Maintenance of the blood pressure until these drugs have had time to stop the arrhythmia serves several vital purposes. As we have seen in the experimental animal, it improves coronary flow, thus reducing the danger of fresh myocardial infarction or extension of an already existing infarct. In addition, maintenance of normal or nearly normal blood pressure levels will minimize the possibility of serious injury to the brain and other important organs.

Our demonstration that the coronary blood pressure and flow are markedly diminished during cardiac arrhythmias suggests that pressor agents should be used promptly for treatment of the cardiac arrhythmias if hypotension occurs, especially in the presence of coronary arteriosclerosis. It is our feeling that, in a patient with impaired coronary circulation, attempts should first be made to stimulate the vagus nerve, e.g., by eveball pressure, carotid sinus massage, induction of the gag reflex, etc. If these measures should fail to restore sinus rhythm, a pressor agent should be promptly given before starting quinidine or cardiac glycosides, because the latter agents are usually slow to take effect. In our experience, the most effective and safest pressor agent has been noradrenalin. The pressor effect of this agent, given by intravenous drip, can be regulated almost at will by varying the rate of administration. The effect of other pressor drugs is less easily controlled, and may last for hours after they are given. If the pressor effect is too profound, ventricular arrhythmias may occur. For this reason it is advisable to use an agent such as noradrenalin whose pressor effect can be quickly limited should the blood pressure rise to dangerous arrhythmiaproducing levels.

SUMMARY

1. Comparative measurements of coronary artery and sinus flow, coronary blood pressure and systemic blood pressure, cardiac output and venous

pressure were made in animals during regular sinus rhythm, premature auricular and ventricular systoles, auricular tachycardia, flutter and fibrillation, and during ventricular tachycardia and fibrillation.

2. Coronary artery flow was often reduced by these arrhythmias. Coronary sinus flow was also reduced but not to the same degree. Transient compensatory mechanisms attempt to maintain myocardial blood supply in rapid tachycardias if the systemic blood pressure and cardiac output are not too seriously compromised.

3. Brachial artery tracings in human patients revealed a significant lowering of systemic blood pressure, similar to those of the experimental animal following premature auricular and ventricular systoles and during auricular

fibrillation, flutter and tachycardia with rapid ventricular rates.

4. Coronary artery flow diminished in a linear fashion as the systemic pressure decreased. Therefore, if hypotension is present during attacks of rapid tachycardia of auricular or ventricular origin, it is advisable to restore the blood pressure with vasopressor drugs until other antiarrhythmic agents take effect.

5. Vasopressor drugs themselves often abolish auricular tachycardia, flutter and fibrillation, ventricular tachycardia and premature auricular systoles promptly.

6. It was found that the antiarrhythmic effect of pressor drugs was not mediated solely through the vagus nerve, but also by a direct effect on the

7. An explanation of the difference between "benign" and "malignant" ventricular tachycardia is offered.

8. Most of the tachycardias studied were found to cause a decrease in coronary flow, or did not maintain coronary flow sufficiently to meet the increased nutritional demands resulting from the tachycardia. They should therefore be treated promptly, especially in patients with coronary artery disease.

ACKNOWLEDGMENTS

We would like to thank Irving and Norman Feintech, Wm. Forman, Beldon Katleman, F. B. Kaufman, Eric Koenig, E. D. Mitchell, Philip Raisin, Dr. Jules Stein and Wm. Wilkerson for their financial support of this study.

Heparin used in this study was kindly supplied by Darwin Laboratories, Los Angeles, and Walker Laboratories, Inc., Mount Vernon, New York.

Noradrenalin (Levophed) was kindly supplied by the Winthrop Laboratories, Inc., New

Noradrenalin (Levophed) was kindly supplied by the Winthrop La York City.

SUMMARIO IN INTERLINGUA

Mesurationes comparative del fluxo coronari, del tension coronari, e del tension systemic de sanguine esseva effectuate in animales in stato de arrhythmia cardiac. Esseva constatate que le fluxo coronari es reducite per inter 9 e 14 pro cento in le presentia de systoles prematur, per circa 20 pro cento in le presentia de flutter auricular paroxysmal, per 35 pro cento in le presentia de tachycardia auricular paroxysmal, per 44 pro cento in le presentia de fibrillation auricular paroxysmal, e per 62 pro cento in le presentia de tachycardia ventricular. Le tension de sanguine aortic

e le tension del circulation coronari anterograde e retrograde (collateral) esseva omnes reducite per le varie arrhythmias cardiac studiate. Drogas vasopressori succede frequentemente a abolir iste arrhythmias e deberea esser utilisate quandocunque simple mesuras, como massage del sinus carotidic etc., non succede a terminar le arrhythmias.

BIBLIOGRAPHY

- Scherf, D.: Alteration in form of T wave with changes in heart rate, Am. Heart J. 28: 332, 1944.
- Scherf, D., and Blumenfeld, S.: Variations of form of T waves in auricular flutter and fibrillation associated with changes in rate, Am. Heart J. 46: 543, 1953.
- Master, A. M., Dack, S., Gubner, R., and Jaffe, H. L.: Differentiation of acute coronary insufficiency with myocardial infarction from coronary occlusion, Arch. Int. Med. 67: 647, 1941.
- 4. Friedberg, C.: Heart disease, 1956, W. B. Saunders Company, Philadelphia.
- 5. Bellet, S.: Clinical disorders of the heart beat, 1953, Lea & Febiger, Philadelphia.
- Corday, E., and Rothenberg, S.: Cerebral vascular insufficiency, Ann. Int. Med. 47: 626, 1957.
- Galbraith, B. T.: Lower nephron nephrosis associated with prolonged shock from ventricular tachycardia, Am. Heart J. 42: 766, 1951.
- Chinsky, M., Shmagranoff, G. L., and Sherry, S.: Serum transaminase activity; observations in a large group of patients, J. Lab. and Clin. Med. 47: 108, 1956.
- Wegria, R., Frank, C. W., Wang, H. H., and Kanter, D. M.: The effect of auricular and ventricular tachycardias on cardiac output, coronary blood flow, and arterial blood pressure, Federation Proc. 12: 151, 1953.
- Wegria, R., Frank, C. W., Misrahy, G. A., Sioussat, R. S., Sommer, L. S., and Mc-Cormack, G. H.: The effect of auricular fibrillation on cardiac output, coronary blood flow and mean arterial blood pressure, Am. J. Physiol. 163: 135, 1950.
- Wegria, R. R., Keating, R. P., Ward, H. P., Dreyfuss, F., Frank, C., and Blumenthal, M. R.: Effect of auricular fibrillation on coronary blood flow, Am. J. Physiol. 160: 177, 1950.
- Corday, E., de Vera, L., Gold, H., and Williams, J. H.: Hemodynamics of coronary circulation in cardiac arrhythmias, Mod. Concepts, Cardiovas. Dis. 27: 493, 1958.
- de Vera, L., Corday, E., and Gold, H.: A method for simultaneous comparison of the antegrade and collateral coronary blood flow, Circul. Res. 6: 26, 1958.
- Corday, E., de Vera, L., and Gold, H.: The effect of systemic blood pressure on the coronary circulation, Am. J. Cardiol., in press.
- Blumgart, H. L., Zoll, P. M., Paul, M. H., and Norman, L. R.: The effect of experimental acute coronary narrowing and occlusion on stimulation of intercoronary collateral anastomoses, Circulation 12: 682, 1955.
- Katz, L. N., and Pick, A.: Clinical electrocardiography. Part I. The arrhythmias, 1956, Lea & Febiger, Philadelphia.
- Levine, H. D., Lown, B., and Streeper, R. B.: The significance of postextrasystolic T wave changes, Circulation 6: 538, 1952.
- Corday, E., and Williams, J. H.: Effect on hemodynamics of site of origin of ventricular tachycardia, to be published.
- Kory, R. C., and Meneely, G. R.: Cardiac output in auricular fibrillation with observations on the effects of conversion to normal sinus rhythm, J. Clin. Investigation 30: 653, 1951.
- Smith, W. C., Walker, G. L., and Alt, H. L.: The cardiac output in heart disease, Arch. Int. Med. 45: 706, 1930.
- Harvey, R. N., Ferrer, M. I., Richards, D. W., and Cournand, A.: Cardiocirculatory performance in atrial flutter, Circulation 12: 507, 1955.

- Eliakim, M., and Braun, K.: Observation on the relations of electrical and mechanical events in cardiac arrhythmias, Am. Heart J. 51: 61, 1956.
- Askey, J. M.: Auricular flutter in association with myocardial infarction, Am. J. Med. 6: 453, 1949.
- 24. Williams, J. H., and Corday, E.: Effect of cardiac rate on coronary flow, to be published.
- Strong, G. F., and Munroe, D. S.: Paroxysmal ventricular tachycardia—with report of an unusual case, Am. Heart J. 19: 486, 1940.
- Mays, A. T.: Ventricular tachycardia of unusually long duration (seventy-seven days), Am. Heart J. 23: 119, 1942.
- Ring, A., and Blankfein, J.: Paroxysmal ventricular tachycardia in an apparently normal heart, Ann. Int. Med. 42: 680, 1955.
- Youmans, W. B., Goodman, M. J., and Gould, J.: Treatment of paroxysmal auricular tachycardia or nodal tachycardia with vasopressor drug, Neo-synephrine, Proc. Soc. Exper. Biol. and Med. 64: 308, 1947.
- Youmans, W. B., Goodman, M. J., and Gould, J.: Neo-synephrine in treatment of paroxysmal supraventricular tachycardia, Am. Heart J. 37: 359, 1949.
- Berger, A., and Rackliffe, R. L.: Treatment of paroxysmal supraventricular tachycardia with methoxamine, J. A. M. A. 152: 1132, 1953.
- Schoolman, H., Pascale, L. R., Bernstein, L. M., and Littman, A.: Arterenol as an adjunct to the treatment of paroxysmal tachycardia, Am. Heart J. 46: 146, 1953.
- Donegan, C. K., and Townsend, C. V.: Phenylephrine hydrochloride in paroxysmal supraventricular tachycardia, J. A. M. A. 157: 716, 1955.
- Shector, W. E., McLaughlin, J. T., and Dowling, C.: Ventricular arrhythmia induced by methoxamine hydrochloride, J. A. M. A. 158: 1025, 1955.
- Chotkowski, L. A., Powell, C. P., and Rackliffe, R. L.: Methoxamine hydrochloride in treatment of paroxysmal supraventricular tachycardia: report of 3 cases, New England J. Med. 250: 674, 1954.
- McGinn, J. T., and Schluger, J.: Levarterenol bitartrate (Levophed) in the treatment of cardiac arrhythmias, Am. Heart J. 50: 625, 1955.
- 36. Gold, H., and Corday, E.: Antiarrhythmic action of pressor drugs, to be published.
- Wolff, L.: The cardinal manifestations of paroxysmal tachycardia, N. E. J. Med. 232: 527, 1945.

HYPERVENTILATION FROM ORGANIC DISEASE*

By PHILIP R. ARONSON, M.D., Norwich, N. Y.

SYMPTOMS of the hyperventilatory syndrome were first described in 1908 by Haldane and Poulton.¹ These physiologists described the typical tingling in the extremities which subsequently became painful during a period of forced breathing. Since then, numerous references have been made to this syndrome, ^{2, 8, 6} which is amply described by Ames.⁹

It was not until about 1945, however, that the hyperventilatory syndrome began to receive widespread attention, with numerous articles describing the classic symptomatology, pathophysiology, therapy and other aspects of this commonly encountered problem.^{3, 4, 7-9} Its neurogenic nature has been stressed.

As a result, clinicians are becoming better acquainted with this syndrome of overventilation resulting in hypocapnia and alkalemia. Its ready recognition and its frequency, however, make it easy to overlook causative or accompanying organic disease. This is especially true if patients hyperventilate for the first time with the onset of the organic symptoms. When symptoms of hyperventilation dominate the clinical picture, it is all too easy to assume that all the patient's symptoms are purely neurogenic, without considering other possible causes. The following case reports are selected to exemplify what may be described as a secondary or symptomatic overventilation, as opposed to primary or neurogenic hyperventilation. The purpose of presenting these case histories is to provoke a higher sense of clinical awareness of this condition, and to expose the pitfalls that obvious functional symptoms can conceal.

CASE REPORTS

Case 1. A 38 year old white woman with essential hypertension had recovered uneventfully from a cholecystectomy and duodenal ulcer, and from panhysterectomy with bilateral salpingo-oophorectomy for endometriosis. For the next five years the patient had no complaints until one night, after an evening of bowling and of heavy eating she was awakened from sound sleep with a sensation of not being able to take a deep breath, numbness and tingling of the upper extremities, numbness about the lips, and vague, aching pains in her chest. When seen she was apprehensive, swallowing large amounts of air and belching profusely. My initial impression was that for some reason the patient had awakened with a startle reaction and had promptly begun to hyperventilate. Further questioning revealed, however, that one of the patient's first sensations upon awakening was a dull, persistent ache along the

*Received for publication June 2, 1958.

From the Medical Department, Chenango Memorial Hospital, Norwich, N. Y., and the post graduate Medical Service of the State University College of Medicine, Upstate Center,

Requests for reprints should be addressed to Philip R. Aronson, M.D., Medical Arts Building, Newton Avenue, Norwich, N. Y.

inner aspects of both wrists. The hyperventilatory symptoms then followed, and certainly soon dominated the clinical picture. The following morning she was still apprehensive and fatigued. An electrocardiogram then revealed the typical pattern of an acute posterior myocardial infarction. In retrospect, I believe that the dull, persistent ache along the inner aspects of both wrists was the most reliable symptom suggesting myocardial infarction. It should be stressed that this was the first time that this patient had ever been aware of any symptoms of hyperventilation. She has recovered from her infarction, but continues to have hyperventilatory episodes from time to time. Some of these attacks are obviously precipitated by emotional stress, while in other instances the causes are not discernible.

Comment: Despite the multiplicity of vague symptoms accompanying hyperventilation, aching of the wrists is not common, but it is frequent in coronary artery disease. The importance of a careful and detailed history is obvious in this case.

Case 2. A 58 year old white woman awakened from a sound sleep with a sensation of nausea, shortness of breath, lightheadedness, and tingling of hands, feet and lips, and she subsequently vomited. She felt better and went back to bed, again assuming the right lateral position and again promptly becoming nauseated with recurrence of the previous symptoms. In addition she now developed a sensation of fullness in her chest. She became short of breath, slept poorly the rest of the night, and the following morning complained of a constant bitter taste in her mouth. There was also mild dysphagia. I examined her that day and found a very large diaphragmatic hernia incarcerated in the thoracic cavity. Careful questioning revealed that this patient had never had any prior gastrointestinal symptoms, nor had she experienced any symptoms suggestive of respiratory alkalemia. Despite symptomatic therapy, her hiatus hernia caused her considerable difficulties, eventually necessitating surgical correction. She convalesced uneventfully and has had neither gastrointestinal nor hyperventilatory symptoms since then.

Comment: This case history demonstrates the known tendency of diaphragmatic hernias to mimic other clinical syndromes.¹¹ It also typifies the ease with which intrathoracic abnormalities may induce overbreathing.

Case 3. A 36 year old white woman had always been in good health until one evening, while sitting in a chair, she suddenly experienced vague discomfort in the lower part of her chest, later described as a bandlike sensation. She also felt a sudden buzzing sensation in the head, numbness and tingling of the hands, lightheadedness, and dryness of the mouth; she then became nauseated and vomited. After vomiting a few times she felt somewhat better, but for the rest of the night had considerable bloating, belching, flatulence and a vague discomfort over the right costal margin. The next morning this discomfort had increased; she felt warm and, when examined, had a temperature of 101° F., tenderness in the right upper quadrant, and a palpable mass tentatively considered to be a distended gall-bladder. Radiologic examination revealed a distended gall-bladder, which was removed uneventfully. Since that time she has had no more episodes of hyperventilation.

Comment: This hyperventilatory episode was probably an early manifestation of acute cholecystitis. Pathologic processes either above or below the diaphragm are known to produce symptoms very similar to those of respiratory alkalemia. Obviously both conditions may occur at the same time.

Case 4. A 25 year old white man was an asthenic, tense individual who had been in good health with the exception of the irritable colon syndrome. One evening during supper he suddenly noted substernal discomfort and a dull ache, very quickly followed by a sensation of faintness and an awareness of being unable to take a deep enough breath, a few sighing respirations, some yawning, sharp twinges of pain over the right anterior chest, air swallowing and belching. After walking for a short time he felt better and went to bed, but slept very poorly that night because of recurrences of these symptoms. In the morning he was seen with typical symptoms of hyperventilation. There were no specific signs of disease. That afternoon, however, the sensation of tightness in his chest increased and he felt even greater difficulty in breathing. He was seen again with findings indicating a respiratory lag and increased resonance over the left upper chest. A thoracic roentgenogram showed a 50% pneumothorax on the left side. This patient's spontaneous pneumothorax undoubtedly precipitated his first recognizable episode of hyperventilation. The lung gradually reexpanded without difficulty. During the last year this patient has had one other very brief hyperventilatory episode, precipitated by a domestic quarrel.

Comment: The discomfort produced by a spontaneous pneumothorax may be very mild. The accompanying apprehension alone could provoke hyperventilation. (In spontaneous pneumothorax we can assume that, in addition to the overventilation of the blood occurring in the sound lung, compensating for the lack of aeration of some blood still passing through the collapsed lung, there can be some noncompensable anoxia which could be responsible for some of the respiratory stimulation.)

Case 5. A 44 year old white male attorney had always been in good physical and emotional health. He stated that he was awakened from a sound sleep by a dream, had difficulty falling asleep again, and got up and walked about the room. It was then that he became aware of discomfort in his chest, a shortness of breath (characteristically being unable to obtain a deep enough breath), cardiac palpitations, faintness, and numbness and tingling of the hands and face. The patient was seen at that time and, aside from the obvious overventilation, no findings could be elicited. The following day, however, he remained in bed because he felt fatigued and still had vague thoracic discomfort. When seen again, he added that in retrospect he thought that one of the first symptoms had been aching of his lower left jaw. Physical examination was still unrevealing, but an electrocardiogram showed the classic pattern of an acute anteroseptal myocardial infarction. He was hospitalized and placed on anticoagulant therapy and oxygen, but nevertheless suffered fairly severe chest pain for the next three weeks. While in pain he had the symptoms of hyperventilation demonstrated previously. I believe that during this period the involved vessel was not completely occluded, since the electrocardiogram showed rather frequently changing T wave patterns in his anterior thoracic leads. At the end of three weeks it appeared that he had finally had a transmural infarction, and his chest pain disappeared from that point on. Since then, and during the last year, he has had no more symptoms of hypocapnia.

Comment: I believe that the hyperventilatory symptoms made early diagnosis of the myocardial infarction extremely difficult. Jaw pain is a well recognized atypical manifestation of coronary heart disease.

Case 6. A 49 year old white man who had always been in good health was first seen because of a sudden sensation of suffocation, faintness, unsteadiness, and awareness of sighing frequently, numbness and tingling of the face and hands, and marked

xerostomia. The clinical picture was assumed to be due to a typical hyperventilatory syndrome, with no demonstrable precipitating cause. Three days later, when the patient was examined thoroughly, he mentioned that an hour or two before his episode of hyperventilation he had had some difficulty in swallowing and digesting a meal. He had never before had any gastrointestinal symptoms or dysphagia. The physical examination was inconclusive, but subsequent gastrointestinal roentgenograms showed a typical esophageal web, with an accumulation of barium above the web. During fluoroscopic examination a high splenic flexure with a large bubble of air under the left side of the diaphragm was seen. Such a finding is consistent with the splenic flexure syndrome. This patient has continued to have periodic episodes of dysphagia and hyperventilation, precipitated by ingestion of solid food. At no other time has he overventilated, nor did he before this illness. Surgical correction is planned in the near future.

Comment: This demonstrates that disturbances of the lower esophagus may produce overventilation. The respiratory disturbance may also obscure esophageal pathology.

Case 7. A 55 year old white man had always been in good health until one afternoon when he suddenly became ill while working. His wife telephoned that the patient had first experienced shortness of breath, then tightness in his chest accompanied by twinges of pain, numbness of one hand, bloating, belching and considerable anxiety. He was seen 10 minutes later in near shock, with a blood pressure of 60/30 mm. of Hg, a pulse rate of 120 with a barely perceptible pulse, pallor, sweating and marked apprehension. The patient confirmed the sequence of symptoms described by his wife, adding that he now had severe interscapular pain. Femoral pulsations could be palpated only on the right side, and before any therapy could be attempted the patient died. Necropsy revealed a dissecting aortic aneurysm with a large left hemothorax.

Comment: Presumably the first manifestations of the aneurysmal rupture produced marked apprehension, expressed by the symptoms of hyperventilation.

Case 8. A 42 year old white housewife had been diabetic for three years, her diabetes controlled quite easily with weight reduction, diet regulation, and 25 units of NPH insulin daily. One day while walking she felt numbness and tingling in both hands; the left hand then promptly felt cold. She became anxious and stopped to rest, but felt she was suffocating and unable to obtain an adequately deep breath. Cardiac palpitations, light-headedness and finally syncope occurred. When brought to the office she stated that she had never before experienced any of these symptoms, and could not attribute them to anything. Subsequent tests, including spinal puncture, revealed some motor and sensory impairment in both upper extremities, considered probably to be due to diabetic neuritis. The patient was seen by a neurologist, who agreed that this was the most likely explanation. Despite numerous therapeutic measures the patient has continued to overventilate frequently, usually while having symptoms of diabetic neuritis. Sedatives, tranquilizers, constant reassurance, forced breath holding and rebreathing have all been unsuccessful.

Comment: In retrospect, it seems that the initial symptoms of the diabetic neuritis precipitated this patient's first hyperventilatory episode, which obscured and confused the symptoms of the underlying disease.

DISCUSSION

Although the hyperventilatory syndrome usually has a neurogenic background, organic disease, especially when of acute onset, can precipitate such an episode. Since the symptoms of hypocapnia may be vague and at times vexingly diversified, they can easily obscure the signs of the underlying organic disease and thereby present a difficult diagnostic problem.

Lewis, has described a few patients who had a definite organic basis for their overventilation. Goldman 18 reports an interesting case of a medical student who experienced an acute attack of gall-bladder colic; he hyperventilated, and found that this seemed to decrease his pain.

Aside from an occasional reference of this type, however, it has not been stressed sufficiently that hyperventilatory syndromes may well have an organic basis, and often one very difficult to differentiate from the symptoms of the hyperventilatory episode itself. Conditions which at times can produce a vague atypical thoracic discomfort, easily misdiagnosed as a symptom of overventilation, include numerous cardiovascular diseases: coronary artery disease, infarction, pericarditis, dissecting aneurysm, cardiac arrhythmia, pulmonary hypertension and pulmonary emboli. Other intrathoracic diseases may include esophageal disorders, hiatal hernia, painful nonsuppurative swelling of costochondral cartilages (Tietze's syndrome), fibromyositis, intercostal neuralgia, a tender xiphoid process and certain breast disorders. Abdominal diseases include cholecystitis and splenic flexure syndrome. Under miscellaneous we may list cervical arthritis or herniated disc, herpes zoster, rheumatoid arthritis of the spine (Marie-Strümpell disease), certain collagen diseases and salicylate poisoning.

The diagnosis of such mixed syndromes is often especially difficult when the patient is first seen on an emergency basis. A patient's first episode of hyperventilation is frequently a terrifying experience that produces panic and necessitates immediate reassurance and empiric treatment. The clinical picture of such hypocapnic alkalemia is often so unmistakable that it may lead the physician to overlook the possible presence of a more serious causative disease. It is therefore essential that a detailed history be taken as soon as possible, stressing the sequence of appearance of all symptoms, no matter how insignificant. Such diagnostic aids as the electrocardiogram and roentgenogram should be utilized when any suspicion exists.

SUMMARY

Various organic diseases can cause a secondary hyperventilatory syndrome whose symptoms may obscure those of the primary disease. This phenomenon can easily result in an erroneous diagnosis of neurogenic overventilation with failure to recognize the more serious underlying condition. Eight such cases are described, including myocardial infarction, hiatus hernia, cholecystitis, spontaneous pneumothorax, esophageal web with the splenic

flexure syndrome, dissecting aortic aneurysm and diabetic neuritis. Recognition of this danger, together with a careful detailed history, is essential.

ADDENDUM

Since this article was submitted, two patients with paroxysmal supraventricular tachycardia were seen for hyperventilatory symptoms.

SUMMARIO IN INTERLINGUA

Le syndrome de hyperventilation con subsequente alcalemia e hypocapnia occurre non infrequentemente como factor dominante le tableau clinic. Le recognition multo general de iste condition como entitate pathologic resulta facilemente in le tendentia de ignorar le causative factores organic. Quando symptomas de hyperventilation domina le tableau, le pathologia precipitatori remane facilemente obscur pro le observator.

Multe acute entitates organic pote producer episodios de hyperventilation e remaner velate per le symptomas de iste ultime. Le lista de tal entitates organic include morbo de arteria coronari, arrhythmias cardiac, pericarditis, embolos pulmonar, e altere problemas cardiorespiratori. Altere morbos thoracic e abdominal que pote precipitar un attacco de hyperventilation include cholecystitis, distension de flexura splenic, accumulationes subdiaphragmatic, tumefaction nonsuppurative del cartilagines costochondral, fibromyositis, neuralgia intercostal, e certe disordines de pectore.

Le facto que multe morbos organic pote causar secundarimente un syndrome de hyperventilation e que le symptomas de iste syndrome pote obscurar illos del morbo primari resulta non infrequentemente in un diagnose erronee de un problema neurotic, con non-recognition del subjacente processo pathologic. Octo tal casos es describite, incluse infarcimento myocardial, hernia de hiatus, cholecystitis, pneumothorace spontanee, membranation esophagee, dissecante aneurysma aortic, e neuritis diabetic. Un cautemente detaliate historia es essential pro evitar le periculo de errores diagnostic.

BIBLIOGRAPHY

- Haldane, J. S., and Poulton, E. P.: The effects of want of oxygen on respiration, J. Physiol. 37: 390, 1908.
- Kerr, W. J., Dalton, J. W., and Gliebe, P. A.: Some physical phenomena associated with the anxiety states and their relation to hyperventilation, Ann. Int. Med. 11: 961, 1937.
- 3. Carryer, H. M.: The hyperventilation syndrome, M. Clin. North America 31: 845, 1947.
- Engel, G. L., Ferris, E. B., and Logan, M.: Hyperventilation: analysis of clinical symptomatology, Ann. Int. Med. 27: 683, 1947.
- Stead, E. A., Jr., and Warren, J. V.: Clinical significance of hyperventilation; role of hyperventilation in production, diagnosis and treatment of certain anxiety symptoms, Am. J. M. Sc. 206: 183, 1943.
- 6. Fraser, R., and Sargent, W.: Hyperventilation attacks, Brit. M. J. 1: 378, 1938.
- Rice, R. L.: Symptom patterns of the hyperventilation syndrome, Am. J. Med. 8: 691, 1950.
- 8. Lewis, B. I.: The hyperventilation syndrome, Ann. Int. Med. 38: 918, 1953.
- 9. Ames, F.: The hyperventilation syndrome, J. Ment. Sc. 101: 466, 1955.
- Machella, T. E., Dworken, H. J., and Biel, F. J.: Observations on the splenic flexure syndrome, Ann. Int. Med. 37: 543, 1952.
- McKell, T. E., and Sullivan, A. J.: Hyperventilation syndrome in gastroenterology, Gastroenterology 9: 6, 1947.
- Ryder, H. W., Shaver, M., and Ferris, E. B.: Salicylism accompanied by respiratory alkalosis and toxic encephalopathy; report of a fatal case, New England J. Med. 232: 617, 1945.
- 13. Goldman, A.: Clinical tetany by forced respiration, J. A. M. A. 78: 1193, 1922.

DEVELOPMENTS IN FIBRINOLYTIC THERAPY FOR THROMBO-EMBOLIC DISEASE * †

By Sol Sherry, M.D., Anthony P. Fletcher, M.D., and Norma ALKJAERSIG, M.S., St. Louis, Missouri

INTRAVASCULAR thrombi in animals may be dissolved by activating the naturally occurring fibrinolytic enzyme system.^{1, 2} In figure 1 (on the left), there is illustrated an experimental thrombus in the femoral artery of a dog five days after its production. The artery is cut in a semilongitudinal fashion, and evidence of early organization of the well formed thrombus is apparent. The section of artery shown on the right in figure 1 was taken from a second streptokinase-treated animal in which an experimental thrombus had been produced. Both specimens were taken after the same interval. The lumen is patent in this second case with only a few shreds of clot remaining.

Since this observation, considerable progress has been made in developing systemic fibrinolytic therapy for use in man. Although this report will describe our endeavors, it should be recognized that somewhat similar studies are in progress in several other institutions, most notably by groups under the direction of Tillett,8 Cliffton,4 Ambrus and von Kaulla.6 Although the individual approaches may differ, and different agents be employed, the ultimate objectives are the same.

COMPONENTS OF HUMAN FIBRINOLYTIC ENZYME SYSTEM

The known components of the human fibrinolytic enzyme system are illustrated in figure 2. The naturally occurring precursor of the fibrinolytic enzyme of serum is referred to as plasminogen or profibrinolysin. presence of a kinase or activator, this normal serum globulin is converted to plasmin or fibrinolysin. Although human plasma, tissue and urinary kinases have been described, streptokinase, a hemolytic streptococcal product, is the best known of the activators and has been used in most laboratories for studies on the system under consideration. Plasmin, also to be referred to as fibrinolysin, is a proteolytic enzyme, resembling trypsin in many respects, particularly in its pH optimum, and the types of links it splits. Although plasmin digests fibrin into several soluble polypeptides, this proteo-

^{*} Received for publication May 12, 1958.

^{*} Received for publication May 12, 1958.

Presented as a Morning Lecture at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 29, 1958.

From the Research Institute, The Jewish Hospital of St. Louis, and the Department of Medicine, Washington University School of Medicine, St. Louis.

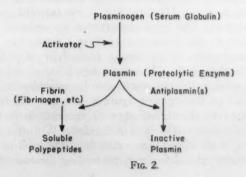
† Supported by grants from the National Heart Institute, National Institutes of Health, and Lederle Laboratories Division, American Cyanamid Company.

Requests for reprints should be addressed to Sol Sherry, M.D., Washington University School of Medicine, 600 South Kingshighway, St. Louis 10, Missouri.



Fig. 1. See text.

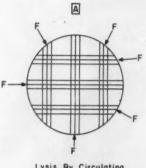
COMPONENTS OF HUMAN FIBRINOLYTIC ENZYME SYSTEM



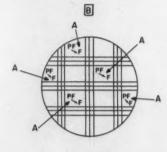
lytic enzyme is not restricted in its action to fibrin but is capable of digesting such additional plasma constituents as fibrinogen, accelerator globulin, and some of the components of serum complement. Free plasmin in blood is rapidly inhibited by one or more antiplasmins found in serum and platelets.

One of the important physical characteristics of plasminogen is its close relationship to fibrinogen and fibrin. Plasminogen and fibrinogen appear simultaneously in areas of exudation, and the concentration of each appears to be correlated. In addition, significant amounts of plasminogen are adsorbed onto fibrin during the clotting process. It is likely that the close relationship between these substances is of considerable physiologic significance.

SCHEMES OF CLOT LYSIS



Lysis By Circulating Fibrinolysin



Lysis By Activation of Intrinsic Profibrinolysin of Clot

Circulating Fibrinolysin Level Critical

Circulating Activator Level Critical

Fig. 3.

MECHANISM OF LYSIS OF THROMBI

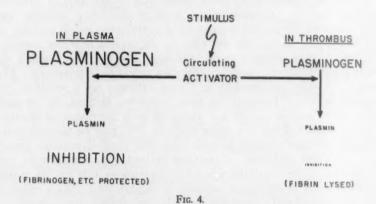
A consideration of the mechanism by which a thrombus is lysed is important both from a physiologic standpoint and in determining an approach to fibrinolytic therapy in man. Until recently it was believed, as shown on the left of figure 3, that clot lysis results from the direct action of circulating plasmin or fibrinolysin on the fibrin meshwork of a thrombus. With this mechanism, the concentration of circulating fibrinolysin is critical in determining the rate of fibrinolysis. However, data accumulated in our laboratories suggest an entirely different mechanism for thrombus lysis. Under this scheme, as shown on the right of figure 3, clot lysis results from the diffusion of activator into the thrombus, with resultant activation of the intrinsic profibrinolysin, followed by lysis of the clot. With this mechanism, the level of activator in the circulation, rather than the level of circulating fibrinolysin, becomes the critical factor in controlling the rate of lysis of a

thrombus. It is beyond the scope of this presentation to present the data which indicate that the level of circulating activator is most critical in determining the rate of dissolution of a preformed thrombus, but the evidence includes studies with different activators and enzymes, a variety of technics, and in vivo as well as in vitro observations.⁷

PHYSIOLOGIC MECHANISM OF FIBRINOLYSIS

A concept concerning the physiologic mechanism of fibrinolysis which has emerged from these studies is summarized in figure 4. The body responds to certain stimuli by releasing activator in or into the circulation. In blood, the strong inhibitory power of the plasma will rapidly inactivate

CONCEPT of PHYSIOLOGICAL MECHANISM for FIBRINOLYSIS (NORMAL PLASMA INHIBITION)



any plasmin formed, protecting the fibrinogen, and other susceptible protein components, from the action of this proteolytic enzyme. On the other hand, diffusion of activator into any fibrin containing exudate will result in activation of the intrinsic plasminogen in a relatively inhibitor-free area, followed by lysis of the fibrin. By this mechanism the fibrinolytic enzyme system is endowed with special fibrinolytic properties, which plasmin itself does not possess. One may also note that, under this hypothesis, the importance of plasminogen in the circulation is not to induce fibrinolysis but to endow thrombi or fibrinous exudate with sufficient plasminogen to mediate its

subsequent lysis.

To test this hypothesis, a study was conducted on patients subjected to procedures known to enhance the fibrinolytic activity of the blood. It was possible to demonstrate that following each of these procedures, which included electroshock, pyrogen therapy, ischemia, exercise and epinephrine

injections, the appearance of enhanced fibrinolytic activity was associated with the release of activator in or into the circulation, yet, as the schema suggests, there were no significant changes in the plasmin or the fibrinogen concentrations of the plasma.

METHODS OF APPROACH TO FIBRINOLYTIC THERAPY

In the development of our studies, consideration was given to four methods by which fibrinolytic therapy might be approached: (1) the use of pharmacologic agents capable of influencing the release of the physiologic activator; (2) the use of purified preparations of known activators; (3) the use of purified preparations of human plasmin, and (4) the use of other proteolytic enzymes capable of hydrolyzing fibrin, e.g., trypsin and chymotrypsin.

As a result of preliminary studies, previously cited, we have concentrated on the level of circulating activator rather than on the level of circulating proteolytic activity. Controlling the level of circulating activator more closely simulates the natural mechanism of fibrinolysis, and is probably less likely to produce undesirable side-effects. At present it is not feasible to control the level of activator by pharmacologic means. Von Kaulla's studies with purified bacterial lipopolysaccharides appear to be promising. These lipopolysaccharides are thought to release activator as a result of their pyrogenic activity. However, in some instances, blocking the pyrogenic reaction with antipyretics has not interfered with the release of activator.⁶

Direct control of the circulating activator level may be accomplished by prolonged infusions of large amounts of highly purified activator preparations. Although urokinase, an activator derived from human urine, probably would be a most desirable agent for this purpose, it is not yet available for patient study in significant quantity, or in pure form. As a result, our studies have developed around the use of highly purified streptokinase.

INTRAVENOUS STREPTOKINASE THERAPY

The streptokinase preparations, recently made available by the Lederle Laboratories, are physicochemically homogeneous, containing only trace impurities on immunochemical analysis. They are well tolerated in patients without pyrogenic reactions. Preliminary observations in animals have shown that considerable success in producing intravascular and extravascular fibrinolysis can be achieved with intravenous injections or infusions of large amounts of streptokinase. Thus, Johnson and Tillett were able to dissolve preformed thrombi in rabbit ear veins, and we have demonstrated in dogs the dissolution of an experimental femoral artery thrombosis, as well as the lysis of fibrin at the site of an experimental traumatic peritonitis.

In patients, therapy has been instituted by the intravenous injection of a priming dose of streptokinase dependent in amount upon the level of circu-

lating antibody, and varying between 10,000 and 200,000 units. Thereafter, the level of circulating activator has been maintained by a sustaining infusion of 30,000 to 100,000 units of streptokinase an hour during the treatment period. This regimen, designed as a consequence of patient studies with isotopically labeled streptokinase, maintains a plasma level of from 3 to 10

streptokinase units per milliliter.

Shown in figure 5, in schematic fashion, are some of the events relating to the fibrinolytic enzyme system which occur in patients during the course of a sustained infusion of large amounts of streptokinase. The first phase, designated the proteolytic phase, is relatively short, usually lasting for about an hour or two. During this period, plasminogen undergoes rapid and complete activation, and free plasmin is liberated in the circulation. As a consequence of the presence of free plasmin, specimens of whole blood removed from the patient will clot and then subsequently lyse. However, since the activator levels are low, specimens of the patient's plasma when placed in contact with preformed fibrin, in the form of fibrin plates, will show little digestion of the preformed fibrin. The second phase, termed the thrombolytic phase, is that period during which the activator concentration reaches and is maintained at a high level. The duration of this period is dependent upon the continuance of the streptokinase infusion. During this period, plasminogen remains depleted, and, by virtue of the action of antiplasmin, all free plasmin has been inactivated. In the absence of plasmin, whole blood specimens fail to lyse. However, because of the high concentration of activator, the patient's plasma will rapidly digest preformed fibrin. The schematic representation shown in figure 5 clearly illustrates the dissociation of the thrombolytic power of the plasma from its plasmin content. This dissociation stems from the fact that the thrombolytic activity of the plasma, i.e., the ability of plasma to dissolve thrombi, is dependent upon the presence of an activator which can diffuse into the thrombus and activate the fibrinolytic enzyme from within. On the other hand, plasmin in the circulation has very little effect on a preformed thrombus, since it cannot activate the intrinsic plasminogen. However, if clotting should occur in the presence of free plasmin, the resulting clot will be digested by this proteolytic enzyme. For these reasons it is unlikely that purified plasmin preparations could be developed for systemic fibrinolytic therapy.

Illustrated in figure 6 are biochemical observations made on a patient with an acute myocardial infarction who received an initial intravenous injection of 100,000 units of streptokinase, followed by a sustaining infusion

of 50,000 units per hour for the next 30 hours.

The upper third of the figure describes the rapid and total activation of the serum plasminogen during the early phase of the infusion, its virtual absence during the rest of the infusion period, and its reappearance following the infusion. Plasma fibrinogen levels fell about 25% during the period of plasminogen activation, or during the time when free plasmin was present

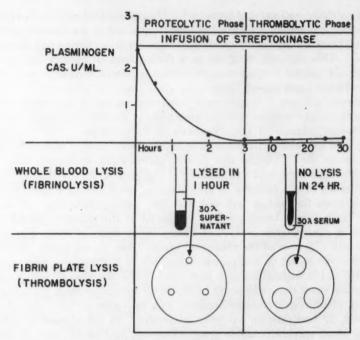


Fig. 5. See text for details.

in the circulation, and then returned toward the normal level despite the continuance of the infusion.

It will be noted in the middle of figure 6 that the thrombolytic activity of the plasma, as measured with radioactive clots or the fibrin plate test, rose sharply in the first hours of the infusion and then was sustained throughout the infusion period. The activity then rapidly decreased when the infusion was terminated.

The lower third of the figure demonstrates the hemostatic defects induced by the intense fibrinolytic state. Special attention has been given to this phase of the study by Alkjaersig, since it was suspected that hemorrhagic complications might prove to be the most serious deterrent to the development of fibrinolytic therapy. As seen in figure 6, the one-stage prothrombin time became moderately prolonged during the streptokinase infusion. This was not attributable to a loss of true prothrombin, as shown by the observations with the two-stage test, but was associated with a moderate decrease in accelerator globulin levels as well as with the appearance of antithrombin activity in the circulation. A diminution in accelerator globulin levels was anticipated, but the appearance of significant antithrombin activity was a surprise. However, the demonstration of this antithrombin activity has been fortunate, for we have been able to block its development by the

ministration of hydrocortisone but without sacrificing any fibrin-lysing activity. In our initial studies with intense fibrinolytic therapy, oozing and ecchymoses at the site of needle punctures were observed fairly commonly, and in a few instances, fresh bleeding occurred at the site of previous operative wounds. In our more recent studies, the simultaneous administration

I.D. ACUTE MYOCARDIAL INFARCTION

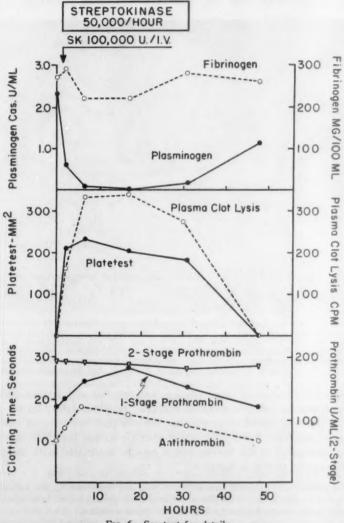


Fig. 6. See text for details.

of hydrocortisone with the streptokinase infusion may have obviated the hemorrhagic diathesis. Not only have patients treated by the new regimen been free of clinical hemorrhage, but also the oozing and ecchymoses formerly found at venipuncture sites no longer occur.

At present, utilizing the technic described, we have treated more than 50 patients with thrombo-embolic disease. Included among these cases are patients with acute coronary thrombosis and myocardial infarction; deep vein thrombophlebitis, with and without complicating pulmonary emboli;

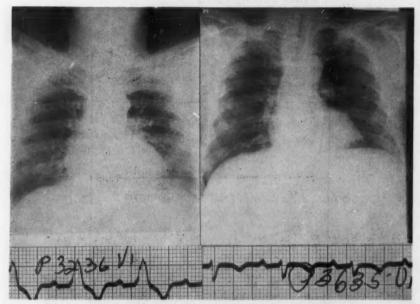


Fig. 7. Effect of 1.7 million units of streptokinase given intravenously over a four-day period on the course of a patient with multiple pulmonary emboli secondary to thrombophlebitis. See text for details. On left, chest x-ray and electrocardiogram (Lead V1) taken immediately before therapy. On right, chest x-ray and electrocardiogram (Lead V1) taken shortly after completion of therapy. (Reprinted, with permission, from Sherry, S., Fletcher, A. P., Alkjaersig, N., and Smyrniotis, F. E., Tr. A. Am. Physicians 70: 288, 1957.)

thrombotic occlusions of large arteries, and arterial and venous occlusions of retinal vessels. Any attempt to evaluate the fibrinolytic therapy in this group of patients would be premature, but evidence has been obtained in a number of instances that intravascular fibrinolysis has been produced.

An illustration of the benefit which may be associated with the fibrinolytic therapy is shown in figure 7.7

The patient, a 61 year old farmer, noted pain and tenderness in the left calf three weeks prior to admission. For the entire two-week period before hospitalization he had been incapacitated by severe dyspnea on minor exertion. Two days before admission he experienced pain in the left inguinal region, followed by tense edema of

the entire left leg. On his admission to Barnes Hospital the left thigh and calf measured 3 cm. more than the right. Chest x-ray and electrocardiogram, shown on the left of figure 7, revealed cardiomegaly and right bundle branch block, presumably as a result of multiple pulmonary emboli. The patient was treated over a four-day period with a total of 1.7 million units of streptokinase. Repeat chest x-ray and electrocardiogram taken shortly after the completion of the streptokinase therapy, as shown on the right of figure 7, revealed a normal heart size and a disappearance of the right bundle branch block. The phlebitis had completely subsided. On subsequent mobilization there was no evidence of diminished cardiac reserve or of post-phlebitic edema.

In the last few months, most of our studies have been confined to one disease, namely acute coronary thrombosis. By restricting these studies to one disease, and by utilizing an appropriate experimental design, we hope that an evaluation of this type of fibrinolytic therapy may be made.

CONCLUDING REMARKS

If these studies with intravenous streptokinase should prove to be successful, systemic fibrinolytic therapy may then be applied to any number of diseases where undesirable accumulations of fibrin occur. The possible scope of fibrinolytic therapy is enormous, not only for the treatment of disease but possibly for prophylaxis as well.

There is little reason to suspect that streptokinase will prove to be the only or the best agent for producing controlled fibrinolysis in patients. Other activators, e.g., urokinase, may prove to be less antigenic and more useful for patient therapy—or perhaps pharmacologic methods for controlling the natural activator level may be developed.

SUMMARIO IN INTERLINGUA

Le presentia del precursor de un enzyma fibrinolytic in plasma human supporta le concepto que fibrinolyse enzymatic es un importante mechanismo physiologic pro disembarassar le organismo de thrombos intravascular. Per consequente, plure gruppos de investigatores se ha occupate de tentativas de disveloppar un therapia directe in casos de morbo thrombo-embolic in humanos per regular le activitate fibrinolytic in le circulation. Al tempore presente, le interesse se concentra primarimente super le uso de partialmente purificate preparatos de fibrinolysina human o de activatores del naturalmente occurrente systema de enzymas fibrinolytic.

Le presente reporto es un revista del componentes del systema de enzymas fibrinolytic in humanos, de recente studios relative al mechanismo que effectua le lyse de thrombos, e del application de iste information in le production de un regulate stato fibrinolytic in le circulation del homine. Le stato currente de iste studios in tanto que illos concerne le therapia de morbo thrombo-embolic es discutite.

BIBLIOGRAPHY

 Johnson, A. J., and Tillett, W. S.: The lysis in rabbits of intravascular blood clots by the streptococcal fibrinolytic system (streptokinase), J. Exper. Med. 95: 449, 1952.

 Sherry, S., Titchener, A., Gottesman, L., Wasserman, P., and Troll, W.: The enzymatic dissolution of experimental arterial thrombi in the dog by trypsin, chymotrypsin, and plasminogen activators, J. Clin. Investigation 33: 1303, 1954.

- Tillett, W. S., Johnson, A. J., and McCarty, W. R.: The intravenous infusion of the streptococcal fibrinolytic principle (streptokinase) into patients, J. Clin. Investigation, 34: 169, 1955.
- 4. Cliffton, E. E.: The use of plasmin in humans, Ann. New York Acad. Sc. 68: 209, 1957.
- Ambrus, J. L., Ambrus, C. M., Back, N., Sokal, J. E., and Collins, G. L.: Clinical and experimental studies on fibrinolytic enzymes, Ann. New York Acad. Sc. 68: 97, 1957.
- Von Kaulla, K. N.: Intravenous protein-free pyrogen; a powerful fibrinolytic agent in man, Circulation 17: 187, 1958.
- Sherry, S., Fletcher, A. P., Alkjaersig, N., and Smyrniotis, F. E.: An approach to intravascular fibrinolysis in man, Tr. A. Am. Physicians 70: 288, 1957.
- Sherry, S., Callaway, D. W., and Freiberg, R.: Prevention of postoperative adhesions in the dog by intravenous injections of plasminogen activators, Proc. Soc. Exper. Biol. and Med. 90: 1, 1955.

PROBLEMS IN THE CORTICOSTEROID THERAPY OF RHEUMATIC DISEASE *

By WILBUR BLECHMAN, M.D., Miami, Florida, and JOHN H. VAUGHAN, M.D., Rochester, N. Y.

HENCH and his co-workers 1 introduced cortisone as a therapeutic agent for the treatment of rheumatic diseases in 1949. Since then this hormone and related derivatives have been extensively used, and their clinical values and limitations have been more fully described.

Although the mechanism of corticosteroid antiphlogistic effect has not been well defined, several observations give us hints as to possible pathways for this action. A general depressant effect of corticosteroids upon nitrogen metabolism can often be demonstrated as a negative nitrogen balance. stances of suppressed cell function, such as the impaired ability of phagocytes to dispose of ingested particles,2 suppressed antibody formation,3 and inhibition of granulation tissue formation in wound healing,4 may possibly be a part of this negative nitrogen balance. One can conceive of the possibility that the antiphlogistic action of corticosteroids is mediated by suppressing some cell function necessary in the normal inflammatory response. Permeability factors have been considered in relation to the antiphlogistic action. It can be shown that the cutaneous tissues and serous membranes are less permeable after corticosteroid therapy.⁵ It has been suggested that the corticosteroids have a direct antihvaluronidase activity.6 During corticosteroid treatment of rabbits with experimental burns, the antiphlogistic activity is accompanied by a decreased sticking of white cells to capillary walls in the areas of the burns, decreased sticking of white cells to each other, and decreased migration through the capillary wall into the area of tissue damage.7 It is of interest that syphilomas in rabbits have a grossly different morbid appearance if the animals are on corticosteroid therapy.8 This has been correlated with the tissue content of sulfate and the inference made that corticosteroids inhibit the incorporation of sulfate into mucopolysaccharides.

Continued biochemical effort has provided many modifications in the steroid nucleus, enhancing one or another of the physiologic expressions of hormonal action.9 Unsaturation of the 1:2 position in the A ring, hydroxylation in the 8 position, reduction in the 22 position, hydroxylation in the 16

^{*}Received for publication May 21, 1958.

From the Connective Tissue Study Group of the Department of Medicine, Medical College of Virginia, Richmond, Virginia.

Supported in part by Research Grant U. S. Public Health Service A-700 of the National Institutes of Health, and by a grant from the Virginia Chapter, Arthritis and Rheumatism Foundation, and the A. D. Williams Fund, Medical College of Virginia, Richmond, Virginia. Requests for reprints should be addressed to John H. Vaughan, M.D., Associate Professor of Medicine, The University of Rochester School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 20, N. Y.

position, halogenation in the 9 position, and methylation in the 6 position all increase markedly the antiphlogistic activity. In some of these instances, however (e.g., the 9 alpha fluoro derivative), a marked increase of saltretaining capacity of the hormone is also seen, making that particular chemical modification of less advantage for use in the treatment of patients with these inflammatory diseases. Other untoward effects, including particularly peptic ulcer formation, ¹⁰ have been seen in greater incidence with other modifications, particularly unsaturation in the A ring (prednisone and Meticorten). Further, the ability to maintain hypercortisonism for longer periods without such limiting factors as salt retention and hypertension has permitted the more frequent development of serious, long-term complications such as osteoporosis and pathologic fractures.

The present report presents case histories of five patients illustrating different problems encountered during the use of corticosteroids. These patients do not represent isolated instances but are part of a general experience which has prompted a more conservative attitude toward corticosteroid therapy in this institution, and has occasioned the belief in this clinic that there should be hesitancy on the part of physicians to institute corticosteroid therapy in all but the most desperate or the most short-termed circumstances.

CASE REPORTS

Case 1. A 64 year old white woman was known to have had rheumatoid arthritis for at least four years. A year and a half prior to the present admission, therapy was begun with Myochrysine and Butazolidin, the response being rather good at first but control thereafter being lost relatively rapidly. Intra-articular hydrocortisone was therefore added to the program. Because of continued difficulty, however, systemic therapy with prednisone, 25 mg. daily, was begun. This was then tapered to 20 mg. daily, which was the minimal dose controlling symptoms. The initial response was excellent, although on continued therapy the clinical effectiveness became much less dramatic. At the same time the patient began to have gastrointestinal symptoms and an upper gastrointestinal series was performed, which failed to reveal any evidence of ulcer.

Four months later the patient developed dark stools and weakness and was rehospitalized. The hemoglobin was noted to be 6.2 gm., and on reëxamination by x-ray a duodenal ulcer was demonstrated. Steroid therapy was discontinued, the patient was transfused, and a rigorous ulcer regimen was instituted. The patient made an uneventful recovery and is presently maintained on salicylates and physical medicine.

Comment: This patient, who was put on steroid therapy for active rheumatoid arthritis, first showed dramatic clinical improvement but subsequently, as is distressingly often the case, failed to maintain this improvement. It was not certain in this instance how much the initial response might have been attributable to psychologic factors. The ultimate development in this patient of massive gastrointestinal bleeding from a peptic ulcer promptly terminated the corticosteroid therapy.

Case 2. A 64 year old white female was admitted to the hospital for attempted "stabilization" of her arthritis. The patient had had rheumatoid arthritis for many years and had been placed on numerous therapeutic regimens. Three years prior to admission, intermittent systemic cortisone therapy had been begun, and for two years prior to admission it was given continuously. Because of persistent disability, how-

ever, it was felt that hospitalization might be profitable.

Physical examination revealed the following: temperature, 99° F.; pulse, 80; respiration, 18; blood pressure, 150/80 mm. of Hg. The patient was a well developed, well nourished white woman, appearing chronically ill, with typical rheumatoid deformities. There was involvement of the knees, ankles, wrists, elbows and metacarpophalangeal joints. Crepitation was present in both knees, and extension was limited at the hips. Laboratory examination revealed a hemoglobin of 11 gm.; white count, 10,000, with 80% polymorphonuclears. Erythrocyte sedimentation rate was 43 to 51 mm./hr.

It was felt advisable to attempt to taper and discontinue cortisone, which was being given in 25 mg. doses three times a day. Consequently phenylbutazone, 300 mg. per day, was substituted. A maculopapular eruption appeared on the inner thighs and the phenylbutazone was discontinued. Salicylates were substituted. The arthritis continued to be quite active. One morning while sitting up on the edge of the bed, the patient noted a "giving away" of her back, followed by the onset of severe pain. X-rays of the lumbar spine revealed marked osteoporosis, with flattening of the second and fifth lumbar vertebral bodies (figure 1).

During the remainder of the patient's hospital course hydrocortisone was utilized intra-articularly, with some benefit. Salicylates and physical medicine were employed. The patient was placed on combined estrogen-androgen therapy. A repeat x-ray at the time of discharge showed some further compression of the L-2 vertebral

body.

Comment: A postmenopausal female arthritic with a two-" to three-year period of corticosteroid therapy developed compression fractures of the lumbar spine secondary to generalized osteoporosis. It seems likely that the steroid therapy contributed significantly to this development. The use of chronic systemic steroid therapy in postmenopausal women is particularly hazardous.

This case also illustrates, as did case 1, an instance where an initial period of greater effectiveness was followed by a period of lack of effectiveness of the corticosteroids in satisfactorily controlling the arthritic symptoms.

Case 3. A 52 year old white male was admitted to the hospital in a semistupor. He had a history of recurrent bouts of joint pains over a 20 year period, the first having been diagnosed as rheumatic fever. The second severe episode was five years prior to admission, at which time rheumatoid arthritis was suspected. The third hospitalization was two years prior to admission, at which time the diagnosis of acute rheumatic fever was again made. This was followed by the institution of systemic corticosteroids, on which he remained continuously until the time of admission. The present illness was marked by the development of progressive mental confusion over a three-week period, culminating in stupor two days prior to admission.

Physical examination revealed: temperature, 104° F.; pulse, 165; respiration, 18; blood pressure, 130/70 mm. of Hg. The patient was a well developed, well nourished white male in a semistuporous condition, responding to painful stimuli only with unintelligible mumblings. The pupils were round and equal and reacted to light and accommodation. Funduscopic examination was negative. There was slight

nuchal rigidity. There was no significant lymphadenopathy. The right lung base revealed diminished resonance and a few moist inspiratory râles. The heart was not enlarged. There was a grade 2 apical systolic murmur. There were slight synovial thickening of both knees and some restriction of movements at the shoulders. There



Fig. 1. Case 2. Extreme osteoporosis of the spine with partial collapse of the second lumbar vertebra.

were slight flexion contractures at the elbows and some limitation of ankle movement. There was a positive Brudzinski's and a questionable Kernig's sign. Babinski's sign was not present.

Laboratory examination revealed the hemoglobin to be 16 gm.; white blood cell count, 13,200, with 82% polymorphonuclears, 12% lymphocytes, 1% basophils and 5% monocytes. The erythrocyte sedimentation rate was 18 mm./hr. Urinalysis was normal. Lumbar puncture revealed an opening pressure of 150 mm. of water. There were 152 cells, 86% lymphocytes and 14% polymorphonuclears. Protein, 128 mg.%; sugar, 17 mg.%, with a simultaneous blood sugar of 115 mg.%. Chlorides, 109 mEq./L. Chest film revealed a mottled infiltration throughout the right lower lobe and mediastinal areas. An electrocardiogram revealed atrial fibrillation and premature ventricular contractions.

A presumptive diagnosis of pulmonary tuberculosis and tuberculous meningitis was made. One gram of streptomycin every 12 hours and INH, 100 mg. three times a day, were begun. Cortisone was slowly reduced but, because of a hypotensive episode, was reinstituted. Combined ACTH and cortisone therapy was then instituted, with gradual reduction and elimination of the latter. The patient was digitalized, and his cardiac rate slowed to 86. During the first 27 days the patient seemed to improve gradually. Tuberculin skin test at 1:1,000 was positive. Several gastric washings were negative for tubercle bacilli, as were spinal fluid cultures. On the twenty-seventh day the patient became worse. Hallucinations developed and the temperature rose to 102° F. A repeat lumbar puncture revealed the presence of large numbers of Cryptococcus neoformans. Thereafter the patient went steadily downhill. In spite of a clearing chest film his semistupor deepened, and he died on the forty-third day of hospitalization.

Comment: This patient with chronic recurrent arthritis developed during the course of maintenance corticosteroid therapy a chronic meningitis which was suspected at first of being tuberculous meningitis but was later identified as cryptococcus meningitis. The infection led to the patient's death. Reduction of the steroid dosage in an effort to allow the patient to develop his normal defense mechanisms more fully was followed by a mild addisonian crisis which necessitated reinstitution of the steroids. This case therefore illustrates two additional difficulties one can encounter in individuals maintained on prolonged corticosteroid therapy.

Case 4. A 26 year old unmarried Negro female who had previously been in good health was admitted to the St. Philips Hospital in May, 1956, because of a rash on the face and hands. This had appeared for the first time several weeks previously. The patient was otherwise asymptomatic. The review of systems and past medical and family histories contributed nothing remarkable.

The physical examination on admission revealed: temperature, 100° F.; respiration, 20; pulse, 90; blood pressure, 120/80 mm. of Hg. Positive findings were limited to a scaling papular rash over both cheeks and nose, a pigmented macular, somewhat scaly eruption over the palmar aspects of the fingers, and a short systolic murmur medial to the apex and along the left sternal border. There was no cardiac enlargement.

Laboratory findings revealed an initial white count of 7,100, which dropped to 2,500 by the time of discharge. There were frequent L.E. cells in a concentrated smear of the peripheral blood. Urinalysis on admission was normal.

Prednisone was begun at a dosage of 10 mg, every six hours. Fever persisted and proteinuria became evident. Although the skin lesions began to fade, the patient

showed progressive mental disturbances, eventually requiring strong-room restraint for mania. Prednisone was continued and gradually reduced to 7.5 mg. daily over a two-week period. Marked clearing of the mental symptoms and of the rash occurred. The patient was discharged on 7.5 mg. of prednisone a day and remained well for nine days. Thereafter she began to vomit, became febrile and anorexic, and developed difficulty in swallowing solids, and some difficulty in breathing, presumably because of too rapid further reduction of the corticosteroid dosage after discharge. On re-admission to the hospital the rash appeared to be healing; there were aphasia, severe ptosis of the lids, and tenderness at the left elbow. Extensor plantar reflexes were noted. A lumbar puncture revealed no abnormality. An electroencephalogram showed a diffuse abnormal pattern suggesting generalized encephalitis.

The patient was put on chloroquine, 250 mg. three times a day. The prednisone was increased to 15 mg. three times a day. The patient improved gradually and was discharged again, and was followed thereafter in the clinic. The prednisone was gradually reduced and then discontinued. The patient presently is asymptomatic 15

months after discharge.

Comment: This patient with systemic lupus erythematosus is presented to illustrate several interesting features. Her disease involved not only diffuse cortical but also bulbar areas of the central nervous system. During her treatment there was considerable discussion and disagreement about whether some of the cerebral symptoms may not have been due to the steroid therapy rather than to the disease. This therapy was continued, however, and the patient improved. It is the general impression in this clinic that, at the dosage here employed, psychotic and convulsive phenomena in active lupus are almost always secondary to the disease and not to the corticosteroid therapy utilized in treatment. Finally, though severely ill during her acute phase, this patient has made a very excellent symptomatic response and now remains relatively well without continued steroid therapy.

Case 5. A 51 year old white married male was admitted to the hospital in September, 1956. He was a known rheumatoid arthritic who had been taking corticosteroids in various forms since 1950. The present illness began with the onset of numbness on the lateral and medial aspects of the feet and up the right leg to the level of the knee. Shortly before admission he also noted scattered red lesions on the legs,

and ulcers developed on both feet.

Physical examination revealed normal temperature, pulse, respiration and blood pressure. There were extensive typical, advanced changes of rheumatoid arthritis involving both hands, wrists, elbows, knees, ankles and feet. On the right foot there was a 2 to 3 cm. ulcer on the dorsolateral aspect. There were purpuric lesions on both feet. Pedal pulses were palpable and equal bilaterally. The ankle jerks were absent bilaterally. There was decreased light touch sensation over the lateral and dorsal aspects of both feet, extending to the knee on the right. Hyperesthesia was noted over the medial aspects of the feet; vibratory and position sense of the toes was decreased. Pain sensation was reduced from the right knee downward and from the left calf downward.

On laboratory examination the only positive finding was a sedimentation rate of 54 mm./hr.

After a period of study and symptomatic therapy the patient was discharged from the hospital. He returned a month later with gangrene of the second and third toes of the right foot and of the lateral surface and heel. ACTH and sulfisoxazole were begun, and a midthigh amputation was performed. The stump healed well, and on continued high ACTH therapy the patient has shown considerable improvement in the remaining involved areas.

Examination of the amputated limb revealed extensive necrosis of the medium sized and small arteries, all three layers being involved with fibrinoid degeneration. There were extensive inflammatory changes in the interstitial layers of the muscle, the muscle fibers themselves showing a myxomatous degeneration.

Comment: A patient with long-standing rheumatoid arthritis and a history of prolonged corticosteroid therapy developed a diffuse angiitis with associated peripheral neuritis and gangrene. This required amputation of

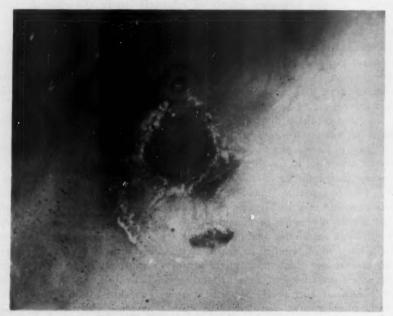


Fig. 2. Case 5. Ulcer of the skin over the first metatarsal head secondary to arteritic tissue ischemia in a rheumatoid arthritic.

the right leg above the knee. There is considerable speculation as to the role of corticosteroids in the development of this type of complication in rheumatoid disease. Diffuse angiitis has often been described in patients on corticoid therapy, but it has also been described in patients without such therapy. Although a high ACTH dosage was accompanied by improvement in the remaining, less involved areas, this does not give a clear indication of whether the corticosteroids contributed to the prior adverse development. Drugs at one dosage level often give rise to one effect and at another dosage level to another effect. It will remain for future observations and investigation to clarify this issue.

DISCUSSION

Demartini, Grokoest and Ragan ¹² have expressed the belief that some degree of induced hypercortisonism is a prerequisite for the effective utilization of corticosteroid hormones in the treatment of rheumatoid arthritis, and it seems probable that this holds also for the other rheumatic diseases. Ragan et al. ¹³ note that such utilization of these hormones constitutes the substitution of one pathologic process for another.

Untoward effects are said to be generally more likely to occur in females * than in males, and are generally related to the cumulative amounts of drugs taken. Though untoward effects of relatively minor consequence, such as hirsutism, obesity, acne and amenorrhea, can be tolerated, others cannot. The tissue-wasting effects, as evidenced by such changes as thinning of the skin, osteoporosis and loss in muscle mass, are serious ones. They are probably expressions of suppressed cellular function, nitrogen loss and glyconeogenesis. Unfortunately there is as yet no encouragement to the persistent hope that the antiphlogistic action of the hormones can be separated from these tissue-wasting effects.

In spite of these difficulties, however, there are instances where the corticosteroids constitute an indispensable therapeutic tool. It is therefore important to have a clear idea of how and when to use them and, most important, when not to use them. Many investigators have suggested certain absolute contraindications to corticosteroid therapy. It is doubtful, however, that this notion should be strictly followed. Often it appears that corticosteroids may be lifesaying, and in such instances one may disregard what would otherwise be considered to be an absolute contraindication. Prophylactic antibiotics against latent or smoldering infections, a vigorous prophylactic ulcer regimen to help prevent reactivation of peptic ulcers, and tranquilizers and sedatives to guard against possible psychotic consequences have often been used in such instances. In patients less critically ill, on the other hand, such problems as these, as well as those of old age, diabetes, history of convulsive disorders, osteoporosis, azotemic nephritis and Cushing's syndrome, would be regarded as more nearly "absolute" contraindications.

Rheumatoid Arthritis: The systemic use of corticosteroids in this disease should be instituted only with great hesitancy. Unfortunately, patients are all too often begun on this therapy without due regard to the severity of the disease or to the unfortunate consequences which may ensue from the therapy. It is now clear that only a rather small proportion of patients undergo a sufficient reduction in underlying disease activity to allow discontinuation of steroids. This has led to a very high incidence of patients entering into long-term therapy, and consequently also to the development of a high incidence of untoward effects among these patients. Peptic ulcers,

^{*}An exception to this is the predominant appearance of the angiitis syndrome (v. infra) in males.

mental disturbances and infection are often early complications, but they may also develop after many months of corticosteroid therapy free from these problems. Osteoporosis with pathologic fracture occurs late. The present policy in this clinic is to begin steroids only as a last resort in patients with overwhelming and progressive disease. The attempt is made to maintain control with salicylates and physical therapy as the first line of approach. The addition of phenylbutazone in maintenance doses of 100 to 300 mg. daily constitutes a secondary approach, and the use of gold salts a third approach.

It is often possible to give symptomatic relief at the major site of incapacity by the intra-articular use of hydrocortisone or prednisolone. 16, 17 Occasionally patients will require such injections less and less frequently, but more commonly the relief afforded lasts only a week or less and the asymptomatic interval fails to lengthen. Nevertheless, in this clinic this therapy has been of great value in allowing control of certain patients otherwise uncontrollable by more conservative means and has allowed earlier initiation and more effective pursuit of physical therapy programs. Such patients do not suffer the deleterious consequences of long-term systemic therapy, although the injection of a severely affected joint often causes some relief of symptoms in other joints distant from the site of injection, suggesting some systemic distribution of the injected material. Psychologic factors, of course, must also be considered in such instances. Hydrocortisone tertiary butyl acetate and prednisolone tertiary butyl acetate are said to be more slowly absorbed from joints than is hydrocortisone acetate, thereby giving more prolonged effects.

A confusing complication in long-term systemic corticoid therapy of rheumatoid arthritis is that of "chronic hypercortisonism," reported by Slocumb 18a, b and by Rotstein and Good. 19 These authors describe the appearance of musculoskeletal and mood symptoms, which they differentiate from those of reactivated rheumatoid arthritis. Chronic hypercortisonism, they believe, can be suspected when musculoskeletal symptoms respond favorably to rest, fail to be clearly located in the joints, fail to respond to physical medicine or salicylates, and are related to mood swings and to a time of day most distant from previous hormone administration. Most important, these patients apparently improve on a gradual reduction in corticosteroid dosage. Although called "chronic hypercortisonism," the true pathogenetic mechanism envisioned is a transient relative hypocortisonism in patients on high dosage, the relatively deficiency occurring during that short period most distantly removed from the last previous dose of medication and just before the next dose. Suppression of normal adrenal function, and therefore a basic underlying hypoadrenalism, are an integral part of the theory proposed.

The problem presented by this concept is twofold. The first is the differentiation of this state from the underlying rheumatoid arthritis. The

second is differentiation from a developing diffuse angiitis 20 such as is illustrated in case 5.21 Slocumb et al. 18a, b also appeared to wonder whether "chronic hypercortisonism" may be related to diffuse angiitis, a condition seen in some of their patients in a form resembling either polyarteritis or lupus erythematosus. Case 2 of Rotstein and Good, 10 and possibly also their case 5, were instances of angiitis. It will be very important for future experience to establish the identity or individuality of these conditions, as upon this will depend the establishment of a proper therapeutic program. Though it has been the experience of this clinic that angiitis developing during therapy may improve following increase in corticosteroid dosage, the explanation for this is not clear. If the "hypercortisonism hypoadrenalism" concept of Slocumb et al. 18a, b be valid, it would seem possible that more vigorous corticosteroid therapy may merely obliterate the transient deficiency phase. The confusion is further compounded by continued uncertainty as to whether the development of diffuse angiitis in these patients represents new disease or a more formidable expression of the original rheumatoid process. It is important to note that polyarteritis was described occasionally 11, 12 in patients with rheumatoid arthritis before cortisone was introduced as a method of treatment.

Bevans et al.²³ have réferred to a diffuse granulomatous angiitis, or polyarteritis, as the "malignant rheumatoid state." Involvement of viscera was extensive in three cases illustrated. High dosages of hormone characterized the case histories. Although it is possible that the corticosteroids may be a significant factor in the development of this extreme state, it is also generally true that only the more fulminating rheumatoid patients are put on high dosage in the first place. The parallelism thus has alternative explanations.

Whether the general experience ^{24, 25, 26} that a very high incidence of peptic ulcer formation occurring in rheumatoid patients on corticosteroid therapy can be related to the basic underlying arteritis of the rheumatoid disease is a fascinating point for speculation. Certainly it is true that there has been no corresponding incidence of peptic ulcers among patients with ulcerative colitis treated with corticosteroids, ²⁷ or in patients with chronic bronchial asthma. ^{28, 29, 30} The problem is analyzed very well by Kammerer et al., ²⁶ who also point out that the peptic ulcers occurring in rheumatoid disease have a high predilection for a gastric rather than a duodenal location. They may occur in spite of histamine achlorhydria and have certain peculiar roentgen characteristics, ²⁵ which distinguish them from ordinary peptic ulcers.

Systemic Lupus Erythematosus: In contrast to the policy of hesitancy with rheumatoid arthritis, systemic lupus erythematosus demands a much more liberal attitude with respect to systemic corticosteroid therapy. Not only is this disease often fatal—it is also one which may rapidly move from a mild, relatively well controlled process into a fulminating, irreversible

downhill course. Corticosteroid hormone therapy should be used early and vigorously when needed. Since this is a disease prone to remission and exacerbation, one is justified in a substantial hope that such therapy can eventually be tapered and even discontinued, sometimes in a period of as little as two or three months. The use of antimalarials as adjunct in such

therapy 31 at present seems promising.

The principal problems encountered in the use of steroids in systemic lupus erythematosus are presented by the renal and central nervous system involvements of the disease. Because of their lack of salt-retaining effect, the preparations unsaturated in the D-1 position have proved to be most useful. Optimally they are employed before any renal involvement at all has demonstrated itself, and in such case there is the hope that the hormone will protect the kidneys from the disease. In cases of minimal renal involvement, one can observe instances of apparent improvement in renal function, and there is the hope of preventing further damage. Where renal involvement is well established, however, corticosteroids not only generally prove to be of no therapeutic value but also may even aggravate the patient's disease, ⁸² either by compounding the kidney pathology with the scars of healing lesions or by complicating the fluid and electrolyte problems.

When a patient with systemic lupus erythematosus has convulsions or evidences psychotic behavior, it is probably much more often true than not that the need is for more rather than less corticosteroid. As is now more and more widely appreciated, involvement of the central nervous system, like involvement of the kidneys, is a major cause of morbidity in this disease. Though the ability of corticosteroids to induce central nervous system symptoms of many varieties is not contested, it is strongly felt that this is seldom the principal cause of the difficulty in patients suffering from acute systemic

lupus erythematosus.

Rheumatic Fever: In the treatment of this disease with corticosteroids, one is faced with a situation similar to that of lupus erythematosus but one in which the heart has taken the place of the kidney. There is no doubt but that one can suppress the signs of acute activity. This is most evident in the response to therapy of acute pericarditis. The influence on chamber enlargement or on the endocarditis, however, is a much more debated point. The ability of the hormones to prevent or to reduce eventual cardiac damage was denied by the Coöperative Study sponsored by the Council on Rheumatic Fever, which reported that ACTH, cortisone and aspirin all led to identical results after two years. Massell, 38 on the other hand, has disputed the significance of these findings, believing that the hormone dosage used in that study was too small.

The program pursued by McCue ³⁴ at the Medical College of Virginia utilizes 300 mg. of cortisone a day for 21 days. The drug is then gradually reduced over the next 40 days. Prednisone is used in one fourth of the dose of cortisone. The last three days of withdrawal are supplemented with

80 mg. Acthar gel each day. This schedule is used only in cases with carditis seen within 28 days of the onset of symptoms. With this therapeutic program in this disease there have been certain differences of emphasis in the problems encountered. Peptic ulcers have rarely been seen among these youngsters. The appearance of fluid retention with ascites, however, has been frequent. Rebound phenomena, which are especially to be avoided because of the possibility of further valvular damage during the exacerbation, have been significantly less frequent with the current two-month course than with the previous one-month course of therapy. The self-limiting features of the inflammation in rheumatic fever of course permit less concern about the long-term drawbacks of corticosteroid therapy in this disease. It is the impression of this group that early institution of corticosteroid therapy does indeed, as claimed by Massell, 33 lower the incidence of residual cardiac damage.

Polyarteritis (Periarteritis nodosum), Scleroderma and Dermatomyositis: The relative infrequency of these diseases has led to a paucity of published experience on their treatment. Definite indications for corticosteroid

therapy have not been established for any of these processes.

Objective improvement has been reported in polyarteritis treated with corticosteroids, but relapses on cessation of therapy have been the general rule.³² The development of widespread infarction as a feature of the intimal proliferation characterizing the healing vascular lesions may possibly prove to be an unusual and lethal result of therapy.^{14, 32} This has been particularly described in relation to the renal lesion.

In scleroderma, corticosteroid therapy offers the least benefit in all the group of diseases being considered. Beigelman et al. 35 observed little or no subjective or objective response among their treated patients. Furthermore, on cessation of therapy there was a high incidence of flare-up, with rapid progression, sometimes leading to early death. Zion et al. 36 have emphasized a similar experience with patients in whom the disease had been of six months' duration or more, and particularly if Raynaud's phenomenon or visceral involvement was already present. In patients with less well established disease, however, the latter investigators reported more encouraging results.

In dermatomyositis, full pharmacologic dosage of steroids (i.e., the dosage which will give at least one of the manifestations of Cushing's disease) has been recommended ³⁷ for a minimum of two to three months. Remissions have occurred which have persisted beyond corticosteroid withdrawal.

In none of these diseases has any improvement been noted once fibrous tissue has been laid down or atrophy has occurred.

Conclusions

The hazards of corticosteroid therapy in rheumatic disease are discussed. Corticosteroids are most advantageously used in those instances where the

basic disease activity tends to be episodic. They are less advantageous in those instances where the basic process tends to be prolonged and unremitting.

SUMMARIO IN INTERLINGUA

Le disponibilitate de hormones corticosteroide pro le tractamento de morbos rheumatic ha providite le clinico con un importante e efficace medio pro lor subjugation. Tamen, al mesme tempore illo ha sublevate problemas de importantia tanto practic como etiam theoric. Le casos presentate in iste reporto servi a illustrar le facto del breve durantia del subjugation clinic in non infrequente casos in que corticosteroides es usate in le tractamento de patientes con active morbos de character refractori e del supervention de hemorrhagias gastrointestinal, osteoporosis e fractura compressional, infectiones intercurrente, episodios de psychose, e le disveloppamento de gangrena. Ben que il non es facile demonstrar un primari relation causal inter le administration del hormones e le adverse reactiones del typo mentionate, le frequentia con que tal reactiones ha essite observate in patientes sub tractamento hormonal indica que le hormones mesme es al minus un major factor contributori. Le diversitate del reactiones se explica le melio super le base del effecto generalmente suppressori que le corticosteroides exerce super le metabolismos anabolic e que resulta in le expression somatic del stato catabolic in le histos conjunctive del subjecto in question, incluse le histos que es concernite con le defensa del organismo contra infectiones. Iste factos ha resultate in le formulation del general principio therapeutic que un therapia corticosteroide debe esser initiate solmente in le caso de statos pathologic in que un comparativemente breve duration del activitate del morbo es multo probabile o in le caso de plus durative statos pathologic quando le circumstantias ha devenite evidentemente desperate.

BIBLIOGRAPHY

- Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: The effect of a hormone
 of the adrenal cortex, (17-hydroxy-11-dehydro-corticosterone; Compound E) and
 of pituitary adreno-corticotrophic hormone on rheumatoid arthritis, Proc. Staff Meet.,
 Mayo Clin. 24: 181, 1949.
- Lurie, M. B., Zappasodi, P., Dannenberg, A. M., Jr., and Cardona-Lynch, E.: The effect of cortisone and ACTH on the pathogenesis of tuberculosis, Ann. New York Acad. Sc. 56: 779, 1953.
- Fischel, E. E.: Hypersensitivity and the hyperadrenal state, in Conference on the connective tissue, edited by C. Ragan, 1952, Josiah Macy, Jr. Foundation, New York.
- Ragan, C.: The effect of ACTH and cortisone on connective tissue, in Conference on the connective tissue, 1950, Josiah Macy, Jr. Foundation, New York.
- Seifter, J., Ehrich, W. E., Baeder, D. H., Butt, A. J., and Hauser, E. A.: Evidence for the direct effect of steroids on the ground substance, Ann. New York Acad. Sc. 56: 693, 1953.
- Opsahl, J. C.: Role of certain steroids in adrenal-hyaluronidase relationship, Yale J. Biol. and Med. 22: 115, 1949.
- Allison, F., Jr., Smith, M. R., and Wood, W. B., Jr.: Studies on the pathogenesis of acute inflammation. I. The inflammatory reaction to thermal injury as observed in the rabbit ear chamber. II. The action of cortisone on the inflammatory response to thermal injury, J. Exper. Med. 102: 655 and 669, 1955.
- 8. Turner, T. B., and Hollander, D. H.: Studies on the mechanism of action of cortisone in experimental syphilis, Am. J. Syph., Gonor. and Ven. Dis. 38: 371, 1954.
- Vaughan, J. H. (Editor): The interim meeting of the American Rheumatism Association, Bull. Rheumat. Dis. 7: 127, 1957.

- Howell, D. S., and Ragan, C.: The course of rheumatoid arthritis during four years of induced hyperadrenalism (IHA), Medicine 35: 83, 1956.
- Ball, J.: Rheumatoid arthritis and polyarteritis nodosa, Ann. Rheumat. Dis. 13: 277, 1954.
- Demartini, F., Grokoest, A. W., and Ragan, C.: Pathological fractures in patients with rheumatoid arthritis treated with cortisone, J. A. M. A. 149: 750, 1952.
- Ragan, C., Demartini, F., Lamont-Havers, R., Jessar, R. A., Vaillancourt, de G., and Grokoest, A. W.: A critical appraisal of current therapy in rheumatoid arthritis, Bull. New York Acad. Med. 28: 493, 1952.
- Robinson, W. D., Boland, E. W., Bunim, J. J., Crain, D. C., Engleman, E. P., Graham, W., Lockie, L. M., Montgomery, M. M., Ragan, C., Ropes, M. W., Rosenberg, E. F., and Smyth, C. J.: Rheumatism and arthritis: review of American and English literature of recent years (tenth rheumatism review), Ann. Int. Med. 39: 572-573, 1953.
- Toone, E. C., Jr., and Irby, R.: Effect of cortisone in the long-term treatment of rheumatoid arthritis, Am. J. Med. 18: 41, 1955.
- Hollander, J. L.: The use of intra-articular hydrocortisone, its analogs, and its higher esters in arthritis, Ann. New York Acad. Sc. 61: 511, 1955.
- Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., Udell, L., Smulker, N. M., and Bowie, M. A.: Hydrocortisone tertiary-butyl-acetate by intra-articular injection, J. A. M. A. 158: 476, 1955.
- (a) Slocumb, C. H., Polley, H. F., Ward, L. E., and Hench, P. S.: Diagnosis, treatment and prevention of chronic hypercortisonism in patients with rheumatoid arthritis, Ann. Int. Med. 46: 86-101 (Jan.) 1957.
 - (b) Kemper, J. W., Baggenstoss, A. H., and Slocumb, C. H.: The relationship of therapy with cortisone to the incidence of vascular lesions in rheumatoid arthritis, Ann. Int. Med. 46: 831-851 (May) 1957.
- 19. Rotstein, J., and Good, R. A.: Steroid pseudorheumatism, Arch. Int. Med. 99: 545, 1957.
- Ragan, C.: The relationship of rheumatoid arthritis to periarteritis nodosa and systemic lupus erythematosus, J. Chron. Dis. 5: 688, 1957.
- Irby, R., Adams, R. A., and Toone, E. C., Jr.: Peripheral neuritis associated with arthritis, Arthritis and Rheumat. 1: 44, 1958.
- Sokoloff, L., and Bunim, J. J.: Vascular lesions in rheumatoid arthritis, J. Chron. Dis. 5: 668, 1957.
- Bevans, M., Nadell, J., Demartini, F., and Ragan, C.: The systemic lesions of malignant rheumatoid arthritis, Am. J. Med. 16: 197, 1954.
- Bunim, J. J., Ziff, M., and McEwen, C.: Evaluation of prolonged cortisone therapy in rheumatoid arthritis, Am. J. Med. 18: 27, 1955.
- Hilbish, T. F., and Black, R. L.: X-ray manifestation of peptic ulceration during corticosteroid therapy of rheumatoid arthritis, Arch. Int. Med. 101: 932, 1958.
- Kammerer, W. H., Freiberger, R. H., and Rivelis, A. L.: Peptic ulcer in rheumatoid patients on corticosteroid therapy, Arthritis and Rheumat. 1: 122, 1958.
- Kirsner, J. B., Sklar, M., and Palmer, W. L.: The use of ACTH, cortisone, hydrocortisone and related compounds in the management of ulcerative colitis: experience in 180 patients, Am. J. Med. 22: 264, 1957.
- Burrage, W. S., Irwin, J. W., and Gibson, J. S.: Maintenance cortisone in severe bronchial asthma, J. Allergy 23: 310, 1952.
- Lowell, F., Schiller, I., Leard, S., and Franklin, W.: Prolonged treatment of bronchial asthma with cortisone, J. Allergy 24: 112, 1953.
- 30. Gilford, H. H.: Prolonged ambulatory use of cortisone and ACTH for bronchial asthma and other allergies, J. Allergy 24: 510, 1953.
- Du Bois, E. L.: Systemic lupus erythematosus: recent advances in its diagnosis and treatment, Ann. Int. Med. 45: 163, 1956.

- Thorn, G. W., Jenkins, D., Laidlaw, J. C., Goetz, F. C., Dingman, J. F., Arons, W. L., Streeten, D. H. P., and McCracken, B. H.: Pharmacologic aspects of adrenocortical steroids and ACTH in man, New England J. Med. 248: 232, 323, 369, 414, 632, 1953.
- Massell, B. F.: Hormone treatment of rheumatic carditis, Bull. Rheumat. Dis. 6: 99-100 (Dec.) 1955.
- 34. McCue, C. M.: Steroid therapy for rheumatic fever, J. Pediat. 51: 255, 1957.
- 35. Beigelman, P. M., Goldner, F., and Bayles, T. B.: Progressive systemic sclerosis (scleroderma), New England J. Med. 249: 45, 1953.
- Zion, M. M., Goldberg, B., and Suzman, M. M.: Corticotrophin and cortisone in the treatment of scleroderma, Quart. J. Med. 24: 215, 1955.
- 37. Talbott, J. H., and Ferrandis, R. M.: Collagen diseases, 1956, Grune and Stratton, New York.

CLINICAL EVALUATION OF FORMAMIDINYLIM-INOUREA, A NEW BIGUANIDE ORAL BLOOD SUGAR LOWERING COMPOUND: COMPARI-SON WITH OTHER HYPOGLYCEMIC AGENTS*

By Leo P. Krall, M.D., and Robert F. Bradley, M.D., Boston, Massachusetts

The search for orally effective hypoglycemic agents preceded the advent of insulin by several years. Although this report evaluates the biguanides and compares them to other hypoglycemic agents, a look at the compounds in earlier use, particularly the guanidines, shows that the roots of the problem go back over 40 years.

THE EARLIER HYPOGLYCEMIC AGENTS

Early observation that tetany resulting from parathyroidectomy was accompanied by hypoglycemia 1 and increased levels of guanidine in the blood 2 led in 1918 to Watanabe's 8 correlation between a marked effect of guanidine on intermediary metabolism and decreased blood glucose levels. Frank, Stern and Nothmann 4 showed that guanidine produced spasms and convulsions in experimental animals, and that these were associated with hypoglycemia which did not readily respond to intravenous glucose injec-Further study of guanidine derivatives led to the finding of a higher homologue, Synthalin,⁵ a deca-methylene-diguanidine (figure 1), which produced hypoglycemia in normal and in diabetic dogs after parenteral or oral administration. Oral Synthalin action took from eight to 12 hours to become effective, but its peak was reached after 24 hours and the duration was three days, thus outlasting the effects of the insulin then available. However, anorexia, vomiting and exhaustion were noted in animals surviving the acute episode. Synthalin decreased glycosuria in human diabetics, and clinical success in some mild and moderately severe diabetic patients was reported for periods of six months or longer.6 However, the maximal tolerated dose was reached quickly, and further increases in dosage were accompanied by anorexia, abdominal discomfort, hyperperistalsis, vomiting and diarrhea.

In this era of insulin's great success there was still a spate of Synthalin

^{*} Received for publication May 12, 1958.

Presented at the Thirty-ninth Annual Session of The American College of Physicians,

Atlantic City, New Jersey, May 2, 1958.

From the Joslin Clinic and New England Deaconess Hospital, Boston, Massachusetts.

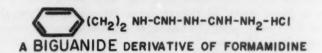
Requests for reprints should be addressed to Leo P. Krall, M.D., Joslin Clinic, 15

Joslin Road, Boston 15, Massachusetts.

reports, and in 1928 Synthalin B (Neosynthalin), differing only in the addition of two methyl groups to its formula, was used therapeutically. Diminished side-effects were claimed, and Synthalin continued to receive support as an oral substitute for insulin. Frank and Wagner noticed that prolonged use of the drug led to a lack of well-being, although gastrointestinal side-effects 9, 10 were diminished by administration of Decholin.

While Synthalin was being used by many investigators, insulin was assuming its physiologically sound position in diabetic treatment, and evidence of Synthalin toxicity, although poorly documented, halted its clinical use. Toxicity was reported primarily as injury to the liver, with jaun-

(DBI) PHENETHYL-FORMAMIDINYLIMINOUREA HCI



(SYNTHALIN) GUANIDINE-DECA-METHYLENE-GUANIDINE

NH2 -CNH-NH-(CH2)10-NH-CNH-NH2

A DIGUANIDINE

Fig. 1. Comparison of chemical structures of DBI and Synthalin.

dice,^{11, 12, 18, 14} acute yellow atrophy ¹⁵ and deranged liver function ¹⁶ in treated patients. Widespread liver and kidney damage was found in rabbits and dogs.^{17, 18}

This latter trend prevailed, and in spite of the apparently successful use of this substance the evidence of toxicity outweighed the benefits of Synthalin; this, coupled with the increasing usefulness of insulin, caused the therapeutic demise of the drug which had raised so many hopes only a few years earlier.

METABOLIC EFFECTS OF SYNTHALIN

The principal metabolic changes induced by Synthalin are: (1) depletion of liver glycogen accompanying hypoglycemia within from two to five hours after Synthalin administration in rabbits, and failure of the disappearing glucose to be oxidized; ^{17, 19} (2) absence of the usual hyperglycemic response to epinephrine ¹⁷ and to glucagon; ²⁰ (3) accumulation of lactic acid in blood ^{17, 21, 22, 28} and greatly increased excretion of it in the urine; ^{22, 28} (4) loss of glycogen from the perfused hind limb of the dog despite increased disappearance of glucose; ^{17, 22, 24} and (5) lowered blood sugar in the eviscerated animal. ^{17, 22} It was claimed that, in the eviscerated preparation, all

of the disappearing sugar could be accounted for by the lactic acid accumulation in muscle.²² These results, indicating actions of Synthalin quite unlike and in some respects opposite to those of insulin, contributed measurably to its elimination from clinical use.

Later, increased blood guanidine levels were reported after transfusions with citrated blood ²⁵ and in chronic renal disease. ²⁶ Toxicity associated with hyperguanidinemia was enhanced by diminished circulating calcium ions, but was effectively reduced by calcium administration. ²⁵ Administration of sodium lactate tended to *increase* the alkali deficit (lowered pH, bicarbonate in blood), and blood lactic acid levels remained high in children with guanidine intoxication. ²⁵ Concluding that increased blood citrate or lactate may lead to formation of insoluble complexes with calcium and thus to greater sensitivity to elevated blood guanidine, Martensson demonstrated striking rises in blood citrate of animals given guanidine or Synthalin. ²⁶ He found that the usually rapid elimination of citric acid was significantly delayed by Synthalin or guanidine.

MECHANISM OF ACTION OF SYNTHALIN

Synthalin has returned briefly to the spotlight in studies of pancreatic alpha cells and the action of glucagon. Hydropic degeneration of the alpha cells in rabbit pancreas ²⁷ and variable initial hyperglycemia, followed by typical hypoglycemia, are produced by Synthalin. ²⁸ Severe toxicity to both kidney ^{28, 29} and liver has repeatedly been confirmed. Evidence clearly ruling out destruction of alpha cells and loss of glucagon as the cause of Synthalin-induced hypoglycemia has recently been summarized. ²⁰ Also, the hypoglycemic effects of Synthalin are evidently *not* produced by liver damage, as was originally believed by many, since histologic changes in the liver may be minimal or absent despite severe hypoglycemia, and are rarely of the degree seen when hypoglycemia is produced by other hepatotoxins. ²⁰

Recent experiments ³⁰ performed on mitochondria prepared from rabbit kidney cortex or rat liver demonstrated that oxidation of glutamate and the Krebs' cycle acids, with the exception of *succinate*, was inhibited in similar manner by guanidine or Synthalin. The effects were confined to oxidations coupled with phosphorylation. The data are interpreted by Hollunger ³⁰ as indicating that either guanidine or Synthalin blocks the oxygen uptake of mitochondria by inhibiting the mechanism that couples oxidation at the

pyridine nucleotide-cytochrome-c level with phosphorylation.

Production of the *metabolic* effects (see above and table 1) can be explained, by the unusually comprehensive data of Hollunger, as being due to increased anaerobic glycolysis.

OTHER HYPOGLYCEMIC AGENTS

There were other substances of lesser repute. Myrtillin, a product of the blueberry plant, while achieving no great acceptance, appeared to improve carbohydrate tolerance.⁸¹ Blotner and Murphy ⁸² made observations showing that oral ingestion of calves' liver preparations caused a definite decrease in blood sugar levels. It was hypothecated that these extracts might contain active hypoglycemic substances, but none was isolated.

A few years later the earliest sulfonylurea findings were being published. 83, 34 These substances, soon leading to extensive use of carbutamide

TABLE 1 Blood Sugar Lowering Agents: Comparison of Metabolic Effects

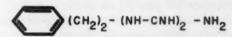
| | Guanidine | Synthalin A and B | Tolbutamide | Biguanide (PEDG or DBI) | Insulin(1) |
|-----------------------------------|---|---|--|---|---|
| Blood sugar lowering | + | + | + | + | + |
| Intact animals | + | + | + | + | + |
| Normal man | + | + | + | + | + |
| Without pancreas | + | + | 0 | + | + |
| Without liver | + | + | + | + | + |
| Glucose uptake in vitro | Inc. | Inc. | 0 | Inc. | Inc. |
| Muscle glycogen in vitro | Dec. | Dec. | 0 | Dec. | Inc. |
| Liver glycogen | Dec. | Dec. | Inc. | Dec. | ± Inc.(9) |
| Hepatic vein glucose output | Dec. | Dec. | Dec. | ± | Dec. |
| R. Q.—Animals | Inc. | Inc. | 0 | Inc. | Inc. |
| R. Q.—Man | ? | ? | 0 | 3 | Inc. |
| Glucagon hyperglyc. | 0 | 0 | + ' | 0 | + |
| Epinephr. hyperglyc. | 0 | 0 | + | 0 | + |
| Lactic acid | Inc. 3+ | Inc. 3+ | 0(a) | Inc. 3+ | Inc. |
| Glucose oxidation | Dec. | Dec. | Inc. | 3 | Inc. |
| Alpha cell damage | 0 | + . | 0 | 0 | 0 |
| Site of action | ? Inhibits oxida- tion at pyridine nucleotide-cyto- chrome-c level | ? Inhibits oxida- tion at pyridine nucleotide-cyto- chrome-c level | 1) Increased (4) insulin secretion 2) Decreased hepatic glu- cose output (5) | ? Inhibits succinic oxidase system ?? Increased peripheral glucose uptake (7) | ? Single action on permeability of cell to glucose ⁽¹⁾ |
| Toxicity or per- manent injury | + | + | 0 | 0, | None other than effects of hypo- glycemia on cen- tral nervous sys- tem |
| Side-effects, man | + | + | Occasional | + | Hypoglycemia |

⁺ Positive response.
0 No response.
Inc. Indicates increased response.
Dec. Indicates decreased response.
0) Ref. 59.
0) Ref. 59.
0) Ref. 60.
4) Ref. 61.
6) Ref. 62.
(9) Ref. 67.
(9) Ref. 67.
(9) Ref. 67.

⁽⁷⁾ Ref. 69. Unless otherwise stated, this summary of changes is based on data cited in the text.

THE BIGUANIDES

(DBI) PHENETHYL-FORMAMIDINYLIMINOUREA



OTHER ANALOGS:

(DBB) NORMALAMYL-FORMAMIDINYLIMINOUREA (DBTU) ISOAMYL-FORMAMIDINYLIMINOUREA (DBC) METHYLBENZYL-FORMAMIDINYLIMINOUREA

Fig. 2.

and tolbutamide, have been well documented 85, 36 in contemporary medical literature for their ability to lower blood sugar in selected diabetic patients.

THE BIGUANIDES

In 1929 Slotta and Tschesche ⁸⁷ reported the oral hypoglycemic activity of some lower alkyl derivatives of biguanide. In 1957 Ungar et al. ⁸⁸ described a later development, N¹beta-phenethylformamidinyliminourea hydrochloride (DBI), which produced a hypoglycemic effect in both normal and alloxan-diabetic rabbits, rats and monkeys. Pomeranze ⁸⁰ demonstrated this same effect in human diabetics, and suggested that part of the action might be due to an increased peripheral utilization of glucose. Krall ⁴⁰ and Williams ⁴¹ corroborated this blood sugar lowering effect, and observed ^{41, 42} that certain of these biguanides were effective in a wide range of diabetics, although these characteristics were accompanied by a frequent incidence of gastrointestinal side-effects.

The present report evaluates the clinical characteristics of four biguanide analogues. These are DBI, the phenethylformamidinyliminourea, and the closely related derivatives: DBB, the normal amyl; DBTU, the iso-amyl; and DBC, the methyl benzyl analogue (figure 2), referred to by others ⁴⁸ as PEBG, ABG and IABG. They vary in degree of blood sugar lowering effectiveness and side-effects (table 2).

TABLE 2

Relative Hypoglycemic Effectiveness and Tendency to Side-Effects of the Biguanides

These are listed in order of effective blood sugar lowering and incidence of side-effects.

| and incidence of side-circles. | |
|--------------------------------|--------------|
| 1. Phenethyl-biguanide | (DBI, PEBG) |
| 2. Normal amyl-biguanide | (DBB, ABG) |
| 3. Methyl benzyl-biguanide | (DBC) |
| 4. Iso-amyl-biguanide | (DBTU, IABG) |

The compounds with the highest degree of hypoglycemic effectiveness also had the greatest incidence of side-effects.

EXPERIMENTAL OBSERVATIONS WITH THE BIGUANIDES

Results with phenethyl-biguanide (PEBG or DBI) are described, since to date most studies are with this biguanide analogue, and observations at the clinical and laboratory level indicate that the biguanide structure is re-

sponsible for the findings.

Animal Results: The greatest number of observations to date are in guinea pigs receiving 15 to 30 mg./Kg. of DBI subcutaneously. $^{38, 44}$ This route gives the most consistent hypoglycemia, although the drug is also effective orally, intravenously, intramuscularly and intraperitoneally. Threshold for its action is reached abruptly, as 15 mg./Kg. produce minimal lowering of blood sugar, and 20 mg./Kg. result by two hours in marked hypoglycemia (true blood sugar falling from 100 to less than 20 mg.%), with \pm 50% animal mortality. $^{38, 44}$ In surviving animals, peak effects on blood sugar are reached at from three to five hours, and duration is less than 24 hours after a single dose of DBI. 46a

All species of laboratory animals given the appropriate dosage show a hypoglycemic response, with the exception of the dog. In the latter animal, blood sugars respond inconsistently, and death occurs in a few days with a normal blood sugar but with elevated serum phosphorus and low serum calcium. This exceptional result in the dog recalls the finding in studies with Paludrine that after this biguanide is given in acute experiments, blood levels at the peak period are from seven to eleven times those found in monkeys receiving comparable dosages. Side-effects also are more pronounced after long term administration of Paludrine to the dog. Since absorption of Paludrine occurs at the same rate in dogs and monkeys, there may be a species difference in the metabolism of this biguanide, and possibly in that of DBI, in the dog.

DBI also lowers blood sugar levels in alloxan-diabetic rabbits, rats and monkeys.³⁸ Higher dosage is often required, and may be tolerated at 800

mg./Kg.

Absorption, Fate and Excretion: Reports of the fate of DBI are not as yet available, but its action by the oral route indicates that absorption is considerable. To date there are no data giving measurements of this

biguanide in tissues, in blood, or in excretory products.

Pharmacology: Knowledge of DBI pharmacology is incomplete, but in many respects its behavior simulates that of another biguanide, N1-parachlorophenyl-N5-isopropyl biguanide (Paludrine, or chloroguanide), 46, 47, 48 a potent antimalarial agent developed by the British in World War II and having extensive clinical use. Although only mild blood sugar lowering is produced by Paludrine 47 at 40 mg./Kg. dosage in animals, and its ultimate metabolic fate remains unknown, behavior of the animals receiving acute and chronic dosage schedules is like that of animals receiving excessive doses of DBI, particularly with regard to the gastrointestinal tract. Termination of the administration of Paludrine, even after sublethal doses have been used,

allows rapid reversal of the side-effects and complete recovery. Furthermore, only transient gastrointestinal symptoms are noted when Paludrine dosages are at levels comparable to those used clinically. No pathologic lesions are found in autopsied animals.

Toxicity:

Acute: Death in hypoglycemia is produced in any animal receiving the appropriate dose of DBI, but no gross or histologic lesions are found.^{38, 44}

Chronic: Alloxan-diabetic rats and monkeys receiving DBI for several weeks in dosages maintaining normal blood sugars show no macroscopic or microscopic lesions at autopsy, 38 except for the pancreatic beta-cell damage caused by alloxan.

Rats on DBI, 50–100 mg./Kg. per day, and guinea pigs receiving 10 to 20 mg./Kg. per day for 10 months, have shown no pathologic abnormalities at autopsy in liver, kidney, spleen, stomach, intestines, pancreas, gonads, adrenals, thyroid, skeletal muscle, heart, bones or brain. When compared with control groups, these animals were shown to have experienced the same mortality and growth curves. Urea nitrogen, cholesterol, calcium, sodium and total protein levels are unchanged, and blood counts remain normal.^{45a}

Increased weight of the adrenals has been noted in guinea pigs after amylbiguanide (DBB) for five and one-half weeks, but is attributed to the metabolic changes resulting from hypoglycemia.⁴¹ No anatomic lesions were found.

For comparison, chronic toxicity studies ⁴⁵ⁿ with Synthalin reveal that all animals so treated show kidney or liver damage. The findings may appear after but three or four days of Synthalin in doses comparable in their hypoglycemic effect to that produced by DBI.

Metabolic Effects of the Biguanides: Although DBI lowers blood sugar in alloxan-diabetic ³⁸ and hepatectomized ⁴⁴ animals, the degree of response is much greater in intact animals. Since glucose uptake by the rat diaphragm is increased, ^{43, 45a, 49} the results at this point suggest an action like that of insulin. However, glycogen is not formed in muscle ^{45a, 49} or liver, ^{50a} but is actually depleted, ⁴⁰ and oxidation of glucose by muscle is decreased. ^{45a} The depression of liver glycogen content is less striking after DBI, 15 mg./Kg. subcutaneously, but after 20 mg./Kg. the glycogen content remains subnormal despite administration of glucose. ⁴¹

Contrary to results after insulin or tolbutamide (table 1), the hypergly-cemic response to epinephrine and glucagon is abolished by prior administration of DBI, and the expected increase in hepatic vein glucose output does not occur. Fall in hepatic vein glucose output occurs after DBI, an effect which is minimal following insulin administration. Since glycogen is not being formed, and nitrogen balance studies reveal decreased nitrogen excretion and urea formation, Nielsen and others suggest that DBI decreases gluconeogenesis, and that this effect may account in part for lowering of blood sugar.

The paradox of increased glucose utilization (fall in blood levels and failure of deposition as glycogen) and decreased glucose oxidation is further confirmed by the finding of a rise in respiratory quotient (R.Q.) in animals despite no increase in expired CO₂ or C¹⁴O₂ ⁴⁹ and a fall in CO₂ produced in muscle.^{50a} Accumulations of lactic acid in vitro and in vivo ^{50a} and of citric acid ^{45a} following DBI administration have suggested to Williams, Tanner and Odell that anaerobic glycolysis is increased.⁴¹ Failure of guinea pig diaphragm, liver and adipose tissue removed from animals previously injected with DBI to incorporate glucose-C¹⁴ into protein or lipid ⁴¹ further narrows the path of glucose disappearance to that of anaerobic glycolysis.

Up to this point the metabolic effects of DBI show a remarkable duplication of those noted after the guanidines, such as Synthalin A and B. On the other hand, comparison with insulin and sulfonylurea (tolbutamide)

actions reveals notable differences (table 1).

Mechanism of Action of the Biguanides: From the data summarized above it is obvious that glucose disappears without glycogen formation following administration of DBI. It is not wasted in urine or feces, and decreased gluconeogenesis can account for but a portion of the glucose lost, since hypoglycemia is still noted (though less marked) after hepatectomy. Insulin I¹⁸¹ degradation is inhibited by DBI, which is not due 49 to the reduction in glomerular filtration that has been shown to occur after administration of DBI. However, no significant role is attributed to this action of DBI in the production of hypoglycemia, 44 nor are the observed metabolic effects consistent with "insulin-sparing."

The enigma of the fate of the disappearing glucose has led to search for inhibition of an enzyme or enzyme system by DBI. Studies of enzymes involved in anaerobic glycolysis and liver glycogen formation have revealed no inhibitory effect, 45a, 49 and observations of the effect of DBI on metabolic transformations in aerobic glycolysis (Krebs' cycle) are conflicting. However, inhibition of cytochrome oxidase by phenethyl-biguanide has recently been reported,52 while in the data of Wick, Larson and Serif 53 the most sensitive site for a metabolic block is between succinate and cytochrome-c. The latter investigators measured the effect of DBI at 0.5 mg, per milliliter on the oxidation of C14-labeled substrates (glucose, acetate, citrate, succinate, fumarate) by rat epididymal adipose tissue. Oxidation of glucose, acetate and succinate was significantly depressed, while much less intense inhibition of citrate and fumarate was noted. With the use of the rat liver succinic oxidase system, oxygen uptake was inhibited by DBI at 0.5 mg./ml. when succinate was the substrate, while with ascorbate as the substrate, oxygen uptake was not impaired. According to their interpretation, the results obtained do not preclude other sites of action at higher concentrations of DBI.

The striking similarity between DBI and guanidine is again evident in that both drugs appear partially to inhibit, within the tricarboxylic acid

Lactic acid does not normally accumulate, as it is rapidly converted to pyruvic acid and thence metabolized via the Krebs' cycle. With this pathway inhibited, lactate may accumulate in tissues to which DBI has gained access and lead to increase in circulating blood lactic acid. It has been suggested that the liver is the principal site for the action of DBI, and that biguanide may not enter muscle cells, thus allowing extrahepatic muscle to oxidize lactate produced in the liver.⁵⁸

Since muscle glycogen is not formed, and blood lactate and pyruvate levels are elevated in fasting and glucose-fed diabetic patients ^{50b} after DBI, it may be that DBI enters muscle cells in relatively low concentration and thus incompletely inhibits aerobic oxidation. If we assume that such occurs, a portion of the increased lactate produced may still be removed by aerobic oxidation, some may be excreted in the urine, and possibly oxidation of lactate occurs in extrahepatic tissues when blood levels are high. ^{45b}

In the absence of data giving tissue concentrations of DBI in animals or man, considerable caution must be observed in applying the above preliminary results regarding site of action to the metabolic changes noted to date. Although these effects are in many respects opposite to those produced by insulin, they have been found in acute experiments with doses of DBI considerably in excess of those used clinically. Furthermore, the metabolic effects after prolonged use of DBI may differ considerably from those obtained after its acute administration.

MATERIAL AND METHODS

During the 17 months from December 1, 1956, to May 1, 1958, 210 patients with diabetes received one of the biguanide preparations. Of these, 173 were studied adequately and comprise the study group. They were previously known or recently diagnosed diabetics who demonstrated post-prandial venous blood sugar levels of over 150 mg. per milliliter (Somogyi-Nelson), or 170 mg.% (Folin-Wu) with glycosuria. Most of the above were hospitalized and ate a weighed diet. Fasting blood and urine sugar determinations were obtained at 7 a.m. daily. Capillary blood was obtained at 11 a.m. and 3 p.m. daily, and urine specimens at 11 a.m., 3 p.m. and 9 p.m. All of the blood sugars were determined by the Somogyi-Nelson method,

TABLE 3

Classification of Cases According to the Blood Sugar Lowering Response to the Biguanides

Group I—SUCCESSFUL: A demonstrable blood sugar lowering effect according to criteria in table 4.

- Group II—DISCONTINUED: This group had a demonstrable blood sugar lowering effect but was unable to tolerate the drug. Discontinued from the series because of side-effects.
- Group III—FAILURE: No demonstrable blood sugar lowering effect in the doses administered.
- Group IV—NOT IN STUDY: This group includes uncoöperative patients, inconclusive results, those under observation with minute doses as part of another study, and certain patients who could not demonstrate diabetic activity during the placebo phase of the study. These are not included in results unless they had side-effects.

and urine sugar by the qualitative Benedict method. Twenty-four hour urine sugar was determined by the quantitative Benedict method. Base line values for bromsulfalein retention, cephalin flocculation, thymol turbidity, bilirubin, alkaline phosphatase, nonprotein nitrogen, white and red blood cell count, hemoglobin, differential white blood count and complete urinalysis were obtained prior to the administration of the biguanides. These studies were repeated at three- to six-month intervals throughout the entire study period.

Patients previously taking insulin had biguanides gradually substituted, while those previously not receiving insulin received one of the preparations under study until either the blood sugar returned to normal levels or the patient was unable to tolerate the biguanide. In every case a weighed diet was a part of the hospital regimen *prior* to the administration of the drug, and this diet was to be continued when the patient reverted to outpatient status.

Because of the known tendency to remission in diabetes, and the effectiveness of proper diet, the evaluation of any therapeutic agent is difficult. For this reason an attempt was made, when possible, to determine the true daily

TABLE 4

Criteria for "Blood Sugar Lowering Effect"

- All patients were on a prescribed diabetic diet prior to and during the evaluation period.
 Those on an out-patient status continued this diet.
- 2. Three types of patients were studied:
 - (a) Those receiving no previous insulin had to show a consistent drop of at least 25% in average blood sugar level while receiving the biguanides. This had to be below the level of 150 mg. % venous Somogyi-Nelson blood sugar values on specimens taken at 11 a.m. and 3 p.m.

(b) Those previously maintained with insulin, who were able to replace this with one of the biguanides, had to maintain blood sugar levels as good as or better than those they

had with insulin.

- (c) Those who were unable to replace their insulin fully with the biguanides had to maintain their status with an insulin dose less than 50% of the original plus the biguanide.
- 3. Proof of active diabetes had to be established in each case by either:
 - (a) A diabetic blood sugar level (postprandial Somogyi-Nelson venous value of 150 mg. % or higher) prior to the trial period, and
 - (b) A return to diabetic blood sugar levels when DBI was discontinued or a placebo substituted for the biguanide in spite of a constant diet.

| MONTHS | 1 | 2 | 5 | 12 | 15 | 16 |
|-------------------|-----|----------------------|------------------|-------------------|----------------|----|
| BLOOD SUGAR MGM.% | 420 | 134 | 87 | 75 | 87 | |
| GLYCOSURIA % | 5 % | 0 | 0 | 0 | 0 | 0 |
| TREATMENT | 0 | INSUL IN IO units | BZ 55 I.O GM. | ORINASE LO GM. | DBI 25 MGM. | 0 |

Fig. 3. Demonstration of spontaneous remission. Case No. 92X, age 60, diabetes duration two years.

insulin requirement. In most instances during the course of treatment a placebo was substituted for the oral hypoglycemic agent to confirm the activity of the diabetes during this study. Some cases were omitted from the study for this reason (figure 3). These patients are evidently in remission but are being further observed.

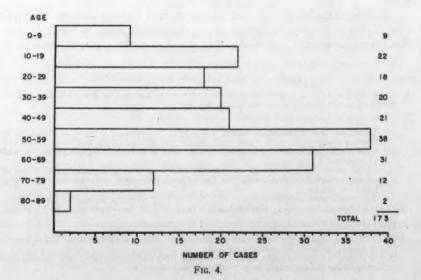
Response to the biguanides was classified into four categories (table 3): successful, discontinued, failure, not in the study. Group I (successful) is that class of diabetics with a demonstrably lowered blood sugar level according to the criteria in table 4. After discharge the patients reverted to outpatient status, with a diabetic diet and the biguanide alone when possible.

Characteristics of the Study Group as a Whole: The 173 patients in the whole study group were selected to include every available type of diabetes.

AGE OF PATIENTS AT ONSET OF STUDY

173 CASES

AVERAGE AGE 43.7 YEARS



DURATION DIABETES AT ONSET OF STUDY 173 CASES AVERAGE DURATION DIABETES 9.8 YES.

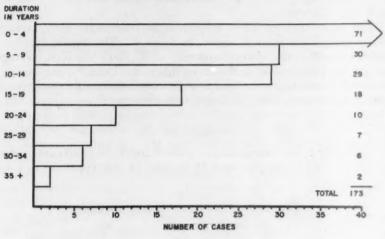


Fig. 5.

AVERAGE DAILY INSULIN DOSE AT ONSET OF STUDY 173 CASES AVERAGE DOSE 37 UNITS

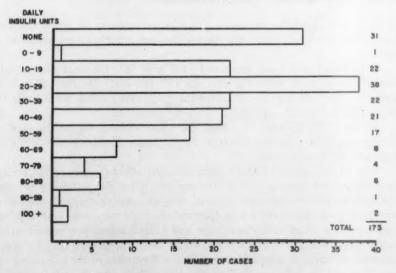


Fig. 6.

Fifty-three (30%) were juvenile-onset diabetics (onset at age 18 or under). Only 32 (19%) were new cases with a diabetes duration of one year or less. Eighty-eight (51%) were adults with known duration of diabetes of from two to 35 years.

Age range was from four to 80 years at the onset of the study, averaging 43.7 years. Distribution is shown in figure 4. The known duration of diabetes varied from "newly diagnosed" to 35 years' duration, averaging 9.8 years. Distribution is shown in figure 5. Prior to this study, 31 patients had been taking no insulin, while in 142 patients the dosage ranged from 5 to 136 units daily, distributed as in figure 6.

RESULTS

According to the criteria cited in tables 3 and 4, the results are as shown in table 5. The 37 cases in Group IV include: 14 observed after single doses

Table 5
Classification of 210 Patients Receiving Biguanides

| Group II Group III | (Successful) (Discontinued) (Failure) | 107 43 23 | (62%) (26%) (12%) |
|-----------------------|---|-----------------|-------------------------|
| Group IV | (Not in study) | 173 37* | (100%) |
| | | 210 1000 | ived biguanid |

²¹⁰ received biguanides

only, 11 with inconclusive results, six with no evidence of active diabetes, four uncoöperative patients, and two with other complications unrelated to diabetes.

If Groups I and II are combined (107 plus 43), the total who actually showed blood sugar lowering effect is 150 (88%). On the other hand, Groups II and III together indicated that 66 (38%) could not tolerate the biguanides in the doses used.

Of the 107 (Group I) cases, 82 still continue biguanide therapy. Exogenous insulin is not required in 57, while the 25 others receive smaller supplemental insulin doses.

The 25 who showed a blood sugar lowering effect (Group I) but are not now taking the biguanide have discontinued it for the following reasons: six were early cases, admitted for trial only and then discharged; six moved to distant places and could not be observed; four did not report with sufficient regularity for valid evaluation; four had complications not related to the study (i.e., heart attack, cerebrovascular accident, major surgery, pregnancy), and three simply did not feel well. Treatment of the remaining two was changed to tolbutamide. In the three "not feeling well," although

^{*} Includes six patients who, though free of side-effects or toxicity, were dropped from Group I because placebo studies showed no active diabetes.

TABLE 6

| Side-Enects in This | Series |
|---------------------|--------|
| Anorexia | 69 |
| Nausea | 55 |
| Vomiting | 29 |
| Metallic taste | 21 |
| Diarrhea | 11 |

^{*} Some patients had multiple side-effects.

blood sugar levels were normal, there was a lack of well-being and a progressive weight loss, which was rapidly reversed on returning to insulin.

The Juvenile-Onset Diabetics: Of the total 173 who received biguanides, 53 (30%) were juvenile-onset diabetics. These include: Group I, 20 cases; Group II, 27; Group III, six; Group IV, none. Nineteen still receive daily biguanide therapy, although only five continue without supplemental daily doses of insulin.

Side-Effects: These frequently occurred, and symptoms were related to the gastrointestinal tract (table 6). These were more annoying than serious, and only 43 (of 173) discontinued the biguanides for this reason. In the face of mild side-effects, some patients continued the therapy and soon tolerated the drug well. Others were free of symptoms with postprandial ingestion of the drug, while in some there was improved tolerance to another biguanide homologue. In every case, the side-effects improved on lowering the dose or on discontinuance of the drug. At times the omission of one or two doses allowed recovery to a point where the drug could be resumed later the same day.

Of the factors evaluated, success or failure with the biguanides appears to be related primarily to the duration of the diabetes (table 7). This is further amplified by the distribution of patients by age, duration of diabetes and daily insufin requirement (table 8).

TABLE 7
Characteristics of Total Study Group Compared with Successful and Unsuccessful Cases

| | Total Study Group (173 cases) | Group I "Successful" (107 cases) | Group III "Failure" (23 cases) |
|--|-------------------------------------|--|--------------------------------|
| Age at onset of diabetes Range Average | 4-80 years 43.7 years | 4-76 years 46.0 years | 11-80 years 49.0 years |
| Known duration of diabetes Range Average | 0-35 years 9.8 years | 0–35 years 7.2 years | 3–33 years 16.5 years |
| Prior to study No insulin Insulin | 31 142 | 27 80 | 1 22 |
| Previous daily dose of insulin Range Average | 5–136 units 37 units | 5–100 units 33 units | 20-136 units 45 units |

The daily maximal dose of biguanides in 107 "successful" cases ranged from 50 to 450 mg. daily (average, 210 mg.), while the later maintenance dose varied from 50 to 300 mg. (average, 150 mg.) in daily divided doses.

The side-effects, when present, usually appeared at the 200 mg. or higher daily dose level for DBI (250 mg. for DBB and 300 mg. for DBTU), although wide individual variations were found. Since the effective level

TABLE 8

Comparative Data Showing the Distribution of Age, Onset of Diabetes and Average Daily Dose of Insulin in the Study Group, Successful Cases and Failure Cases

Age of Patient at Onset of Study

| Age in Years | Total Study Group (173 cases) | Group I Successful (107 cases) | Group III Failures (23 cases) |
|--------------|-------------------------------------|--------------------------------------|-------------------------------------|
| 0-9 | 0 | 5 | 0 |
| 10-19 | 22 | 7 | 3 |
| 20-29 | 18 | 10 | 2 |
| 30-39 | 20 | 11 | 3 |
| 40-49 | 21 | 19 | 0 |
| 50-59 | 38 | 29 | 7 |
| 60-69 | 31 | 21 | 3 |
| 70-79 | 12 | 5 | 4 |
| 80-89 | 2 | 0 | 1 |
| | . — | - | |
| | 173 | 107 | 23 |

Duration of Diabetes at Onset of Study

| Duration Diabetes, in Years | | | |
|-----------------------------------|-----|-----|-----|
| 0-4 | 71 | 55 | 1 |
| 5-9 | 30 | 19 | 5 |
| 10-14 | 29 | 15 | 6 |
| 15-19 | 18 | 8 | 4 |
| 20-24 | 10 | 5 | _ 1 |
| 25-29 | 7 | 3 | . 3 |
| 30-34 | 6 | . 1 | 3 |
| 35 plus | 2 | 1 | 0 |
| | | | _ |
| | 173 | 107 | 23 |
| | | | |

Average Dose of Daily Insulin at Onset of Study

| Units of Daily Insulin | | | | |
|------------------------------|----|------|-----|----|
| No previous | | | | |
| insulin | | 31 | 27 | 1 |
| 0-9 | | 1 | 2 | 0 |
| 10-19 | | 22 | 17 | 0 |
| 20-29 | | 4 38 | 20 | 7 |
| 30-39 | | 22 | 14 | 3 |
| 40-49 | | 21 | 10 | 2 |
| 50-59 | | 17 | 8 | 3 |
| 60-69 | | 8 | 4 | 2 |
| 70-79 | | 4 | 2 | 1 |
| 80-89 | | 6 | 2 | 3 |
| 90-99 | | 1 | 0 | 0 |
| 100 plus | 8" | 2 | 1 | 1 |
| | | | | |
| | | 173 | 107 | 23 |

averaged from 0 to 50 mg. less than this dose, the range between therapeutic dose and that producing side-effects was frequently found to be narrow.

In spite of these side-effects, 82 patients have received one of the biguanide preparations for periods of from four to 17 months. The average duration of treatment is 12 months, while 52 have been observed for longer than one year.

DISCUSSION

In any evaluation of a subject as complex as the action of the biguanides in diabetes, we must answer four questions:

- 1. Do they lower the blood sugar level?
- 2. Are they toxic in the therapeutic dosage?
- 3. Are they suited to long-term therapy?
- 4. What is their clinical value?

These are important, because a negative answer to any of the first three questions makes the succeeding question purely academic. These are also applicable to other oral hypoglycemic agents, since insulin has long since surmounted these obstacles.

1. Do the biguanides lower the blood sugar level?

Our series shows that this is accomplished in a wide variety of cases. In the following case reports, all blood sugar values are reported as milligrams per 100 ml. of blood using the Somogyi-Nelson true blood sugar method.

CASE REPORTS

Case 2. A 56 year old, obese female with diabetes of two years' known duration was admitted to the hospital. Her diabetes was controlled with a diet of 122 gm. of carbohydrate, 58 gm. of protein and 46 gm. of fat, as well as 58 units of NPH insulin daily. After stabilization, 150 mg. of DBI daily were substituted for the insulin, with the following results:

| | | | Blood Sugar | | |
|------------------|----------------------------|----------------------|---------------------|------------------------|--------------------------|
| Hospital Day | Insulin Units | DBI, mg. | Fasting (Venous) | 11 a.m. (Capillary) | 3 p.m. (Capillary) |
| 1 2 8 9 | 58 NPH 58 NPH 0 0 | 0 0 125 175 | 122 133 | 203 | 124 100 149 116 |

The patient was discharged on the thirteenth hospital day and followed as an outpatient. Two weeks later the blood sugar was 104 mg.% two hours postprandial. DBI was then discontinued for several days and the blood sugar level increased to 195 mg.% two and one-half hours after meals, with glycosuria, after which DBI,

75 mg. daily, was resumed. Five months later DBI was again discontinued for five days and the patient was re-admitted to the hospital for evaluation.

| | | Blood Sugar | | | | |
|--------------|----------|---------------------|------------------------|-----------------------|--|--|
| Hospital Day | DBI, mg. | Fasting (Venous) | 11 a.m. (Capillary) | 3 p.m. (Capillary) | | |
| 1 | 0 | | garage. | 235 | | |
| 2 | 175 | | 217 | 159 | | |
| 3 | 200 | 148 | 134 | 120 | | |
| 4 | 150 | 130 | 121 | - | | |

The patient was discharged with the previous diet and 100 mg. of DBI daily. Outpatient treatment was continued for one year, and the diabetes was controlled except during the placebo substitution periods, when hyperglycemia and glycosuria resulted. After one year of DBI therapy the patient has remained well controlled, has lost 12 pounds, is active and feels well. She has suffered no side-effects, and all laboratory tests, including liver, renal and hematologic studies, have remained normal.

Comment: This case illustrates an obese patient with relatively easily controlled diabetes of short duration who probably was taking an unnecessarily high dose of insulin, but was able to replace this with phenethylbiguanide and remain well controlled during the one-year observation period.

Case 88. A tall, thin, 33 year old male had severe, labile, juvenile-onset diabetes with a known duration of 20 years, and was taking 68 units of NPH mixed with 8 units of crystalline insulin before breakfast and 6 units of NPH at bedtime. His diet was 187 gm. of carbohydrate, 87 gm. of protein and 97 gm. of fat. He had many severe hypoglycemic episodes, often without warning.

Even during hospitalization under ideal conditions he still suffered severe reactions. His insulin dose was lowered, with partial substitution of DBI.

| | | | Blood Sugar | | |
|--------------|---------------|----------|---------------------|------------------------|-----------------------|
| Hospital Day | Insulin Units | DBI, mg. | Fasting (Venous) | 11 a.m. (Capillary) | 3 p.m. (Capillary) |
| 2 | 80 70 | 0 | 91 117 | 46 152 | 121 |
| 6 | 30 | 150 | 100 | 70 | 51 |
| 11 | 26 | 200 | 262 202 | 47 85 | 64 |

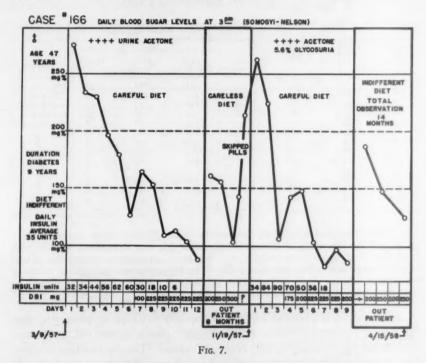
The patient returned to out-patient status with the same diet and 20 units of insulin daily plus 200 mg. of DBI in divided doses.

During the intervening year his urine tests have shown a Benedict's reaction of blue or green, and his interval venous blood sugar tests have shown postprandial levels of 142, 112, 153, 112 and 71 mg.%. There have been only minimal hypoglycemic reactions.

When rehospitalized after one year of observation the patient was adequately controlled with a diet of 192 gm. carbohydrate, 97 gm. protein, 83 gm. fat, 28 units of

insulin daily and 300 mg. of DBB. He has lost four pounds, has a good sense of well-being, and shows no changes in his hematologic or liver function studies.

Comment: This depicts a severe, labile juvenile diabetic who could not be regulated without some insulin in addition to the biguanide, but who takes greatly reduced amounts of insulin, is now free of severe reactions, and appears to have a more stabilized diabetes.



Case 166 (figure 7). This 48 year old male, 73 inches tall and weighing 198 pounds, had a known diabetes duration of eight years. His daily insulin dose was 25 units of NPH daily. He was hospitalized with a diet of 161 gm. of carbohydrate, 88 gm. of protein and 83 gm. of fat. During this hospitalization, 300 mg. of DBTU successfully replaced the insulin. During the next eight months his control was adequate with a 1,900 calorie diet and 200 mg. of DBTU daily. Marked glycosuria was noted during a placebo period. He also became careless with his diet and biguanides, omitting them and taking them only when he had "bad tests." He was found to be in early acidosis, with 4 plus urine acetone, glycosuria, 5.6%, and a fasting blood sugar of 220 mg.%. He was hospitalized and again regulated, although he required as much as 96 units of insulin on one day.

Comment: Since discharge this patient's control has been adequate with no insulin, a diabetic diet and varying doses of biguanide daily. After one year there is no evidence of toxicity.

Case 140. A 55 year old male with known diabetes of 22 years' duration had an extremely labile form of the condition, much like that seen in juvenile diabetics. There were wide fluctuations in blood sugar levels. Within three months of this admission the patient was hospitalized for diabetic coma and treated for hypoglycemia resulting in two hours of unconsciousness. At this time he was hospitalized with diabetic acidosis. Admission blood sugar was 446 mg. per 100 ml.; blood CO₂ 12 mEq.; glycosuria, 6.0%; urine acetone 4 plus. The patient was given 60 units of crystalline insulin at once. His hospital course was as follows.

| Hospital Insulin | Insulin DRI | DBI, | | Blood Sugar | | | Urine | |
|------------------|-------------|------|---------------------|------------------------|-----------------------|------------------------|---------|--|
| Day | Units | mg. | Fasting (Venous) | 11 a.m. (Capillary) | 3 p.m. (Capillary) | Glucose per 24 Hrs. | Acetone | |
| 2 | 32 | | | 321 | 214 | 63 | ++++ | |
| 4 | 48 | - | 324 | 450 | 195 | 73 | ++++ | |
| 5 | 32 | - | _ | 196 | 82 | 12 | +++- | |
| 6 | 24 | | | 250 | 139 | 25 | ++++ | |
| 8 | 32 | | _ | 355 | 177 | 28 | ++++ | |
| 11 | 30 | | 126 | 133 | | 5 | + | |
| 14 | 16 | 100 | _ | 157 | 27 | 11 | Ó | |
| 15 | 16 | 150 | _ | 293 | 161 | 27 | 0 | |
| 16 | 14 | 150 | - | 100 | 53 | 1 | 0 | |
| 17 | 12 | 100 | _ | - | 42 | 2 | + | |
| 18 | 10 | 150 | - | 110 | 86 | 2 | 0 | |
| 19 | 8 | 150 | | 60 | | 0 | 0 | |
| 20 | 8 | 150 | | | - | 0 | 0 | |

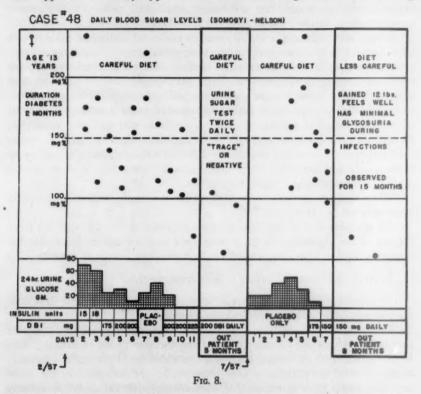
The patient was discharged from the hospital with a diabetic diet, insulin, 6 units daily, and 150 mg. daily of phenethyl-biguanide. He was maintained with normal blood and urine sugars for two weeks, with freedom from reactions during this period, although there was a decrease in appetite. The biguanide was discontinued because the patient left the state for a prolonged vacation. He was returned to insulin with the daily requirement stabilized at 28 units daily.

Comment: This patient represents the severest type of labile diabetes. He was a known sulfonylurea failure and difficult to control under any circumstances, including a rigid hospital routine. The biguanides stabilized him during an observation period. Even during this time, insulin could not be omitted, although he required but 6 units daily. Lente insulin was used at bedtime because of the inability of the biguanide to act through the night in this severe diabetic.

Case 48 (figure 8). This represents a 13 year old girl with diabetes of recent onset. Her blood sugar became stabilized with DBI, 200 mg. daily, plus diet. These values became elevated when a placebo was substituted for the biguanide while the patient was still following a weighed diet, and returned to normal when the oral medication was resumed. After several months of out-patient observation, the biguanide was discontinued for several days. During this period she ate a weighed diet, but hyperglycemia and glycosuria were again found. These returned to normal levels with a resumption of the DBI. She has been observed for 16 months and has maintained good diabetic control and well-being, as well as proper growth and development.

Comment: It must be noted that, although this juvenile diabetic is not in remission and has good control with the biguanide, she did not show urine acetone during the placebo period, although she did manifest hyperglycemia. Her true daily insulin requirement is probably about 20 units daily.

Our results, with the findings of Pomeranze, ⁶⁸ Williams, ⁴⁸ Weller ⁶⁴ and Skillman, ⁶⁵ indicate that the biguanides lower blood sugar levels. This has been apparent in many types of diabetes, including mild diabetes, long



duration cases, labile juvenile types and depancreatized humans, ⁶⁶ when the biguanide is tolerated. It is apparent that in many of the patients with diabetes of the longest duration and greatest severity (as in juveniles), the blood sugar frequently cannot be maintained at normal levels without some insulin. These drugs moreover have not lowered the blood sugar in every case. This may be due to (1) occasional ineffectiveness of the drug, (2) inability to administer an effective dose without side-effects, or (3) possible inabsorption of the drug.

There has been a noteworthy lack of severe hypoglycemic reactions in spite of occasional very low blood sugar levels. There were no cases of

hypoglycemic unconsciousness in spite of blood sugars as low as the one instance of 22 mg. per milliliter. This patient was receiving combined biguanide and insulin, and it is possible that this milder form of hypoglycemic reaction is due to a gradual decrease of blood sugar level.

2. Are the biguanides toxic in the therapeutic dosage?

This question assumes great importance because of the earlier Synthalin experience. Apparently that substance manifested potent hypoglycemic activity, only to fail because of reported toxicity.

In the acute and chronic toxicity studies presented earlier, no toxic effects were found. In our own series of diabetic patients there have been no significant changes in the liver function studies, which included bromsulfalein retention, alkaline phosphatase, cephalin flocculation, thymol turbidity and blood bilirubin. Hematologic studies, including hemoglobin determination, white blood count and blood differential counts, were consistently normal, while renal function studies, including nonprotein nitrogen and urinalysis, showed no variation from normal. It is significant that this lack of change occurred even in some of our patients who had kidney damage secondary to nephropathy and abnormal liver function values secondary to liver disease prior to administration of these biguanides.

These findings, as well as normal serum transaminase levels, have also been reported by others. 41, 48, 68, 68

All available data at this time show no evidence of toxicity resulting from the use of the biguanides in these doses, nor is there any evidence that the relatively high incidence of side-effects is in any way related to toxicity.

3. Are the biguanides suited to long-term therapy?

At present a final answer awaits later clinical experience and data concerning metabolic effects after prolonged therapy.

Resemblance to Synthalin A and B is striking when acute and subacute metabolic changes are considered, but from the standpoint of toxicity there is no similarity. A comparison of biguanides and Synthalin inevitably brings to mind the experience with tolbutamide and carbutamide, the sulfonylureas which show a remarkable resemblance until variations in toxicity are considered. The wide margin of safety of Paludrine indicates that biguanide per se is not inherently toxic at therapeutic levels.

In view of gastrointestinal side-effects that are both rapidly reversible and dose-related, suggesting a relationship to metabolic changes produced by the biguanides, their clinical use requires great care if ill effects are to be kept at a minimum. This is especially so in the initial period of regulation, whether biguanide alone or biguanide plus a reduced insulin dose is used. Even during hospitalization, repeated visits to the patient in any one day may be required. Outpatient coöperation is mandatory with regard to frequent urine tests for sugar and occasionally for acetone, the taking of biguan-

ide exactly as ordered, prompt reporting of ill effects or glycosuria, and regular visits to the physician.

Treatment of diabetes with biguanides is limited. Many of the physiologic effects of insulin are lacking, and biguanides cannot handle the emergencies, such as diabetic keto-acidosis, associated with marked insulin deficits. Some insulin, endogenous or exogenous, is needed in all diabetics receiving biguanide therapy, and this basic requirement for insulin, albeit reduced, is illustrated by certain juvenile-onset diabetics who have satisfactory blood sugar levels and whose insulin dosage has been reduced by 75%, but who may rapidly go out of control as the last 10 units of insulin are further reduced or omitted. In one instance (case 49) a previously omitted insulin dose had to be resumed. A 46 year old male with a known duration of diabetes for one year had been taking 30 units of insulin daily; when they were replaced by 150 mg. of DBI, adequately normal blood sugars resulted. During 11 months of therapy, however, he lost 10 pounds and lacked a sense

TABLE 9
Criteria for Control

| | Degree of Control | | | | |
|-----------------------|--|--|--------|--|--|
| Relation to Food | Good Blood Sugar mg./100 c.c. | Fair Blood Sugar mg./100 c.c. | Poor | | |
| Fasting | 110 | 130 | | | |
| 1 hr. p.c. | 150 | 180 | All | | |
| 2 hr. p.c. | 130 | 150 | others | | |
| 3 hr. p.c. | 110 | 130 | | | |
| Urine sugar in 24 hr. | 2 gm. | 5 gm. | | | |
| | or less | or less | | | |

of well-being and energy. He was always exhausted, although apparently well controlled and although all liver and kidney function tests, as well as hematologic studies, were completely normal. Insulin improved his status rapidly.

Caution is advised in administering insulin to diabetic patients receiving biguanides. As little as 4 to 8 units of insulin may strikingly lower hyperglycemic levels to normal or hypoglycemic ones within four hours.

In the present experience, many patients tolerate the biguanides well and show improved tolerance in the weeks and months following the period of regulation. Weight is maintained, and growing children have thus far (up to one year) maintained normal growth curves. Placebo trials confirm in many instances the need for biguanide therapy for continued control of blood sugar, which is frequently obtained without added insulin.

Control of diabetes has been satisfactory in many instances. When the strict criteria used by Marble (table 9) ⁶⁷ in evaluating tolbutamide were applied, Group I diabetics (total, 107) were rated as having "good" control in 64, "fair" in 31, and "poor" in 12. Although a significant number of

patients in this group had mild- or short-duration diabetes, some of those with extremely labile diabetes obtained striking results that could be classified as "good."

In 31 of the 173 study cases, sulfonylureas had been tried and had failed. With adequate biguanide therapy, the response was as follows: Group I: successful, 19; Group II: discontinued, six; Group III: failures, four; Group IV: not in study, two. It must be stated, however, that these cases represent the type of diabetic for whom the sulfonylureas are obviously contraindicated.

On the other hand, biguanides clearly fail to produce several of the beneficial metabolic effects consistently reproducible with insulin. Regardless of this, increasing numbers of patients having diabetes with juvenile onset or marked lability are faced with rapid rises and falls in blood sugar, often defying the most skillful efforts at control. In these patients, regulation with biguanide and small doses of insulin has in a number of cases smoothed the blood sugar pattern and greatly reduced severe hypoglycemic reactions, with blood sugar control superior to that obtained with insulin alone. The question as to whether such blood sugar lowering is of value from the standpoint of preventing infections and vascular complication on a long-range basis has no answer. For this group of patients, today's existence may be measurably improved.

4. What is the clinical value of the biguanides?

Before attempting to apply the biguanides to the treatment of any segment, large or small, of the diabetic population, one must be prepared to use the precautions already cited. Furthermore, the considerable number of obese, mild diabetics well controlled with diet require no additional treatment, and those in whom adequately decreased diet and weight can be expected to result in well controlled diabetes may require a blood sugar lowering agent only temporarily or intermittently.

If one defers for the present the unknowns in prolonged therapy with biguanides, the clinical value of these and other oral agents should in the strictest sense equal or approach the benefits to be gained with insulin in terms of its day-to-day usefulness. One can reason that biguanides fit these criteria in the severe, labile diabetic, who may carry on his daily activities and work in a much safer and happier fashion, even though he may require one or two small doses of insulin each day.

For the remaining middle segment of diabetics, those requiring more than a proper diet for adequate control of diabetes, any hypoglycemic agent seems at first glance to offer dubious benefits in comparison with insulin when the above strict criteria are used.

On the other hand, tolbutamide has gained considerable repute in the treatment of selected milder diabetics. This has been accomplished by demonstration that this preparation is free of significant toxic side-effects,

and also can maintain adequately lowered blood sugar levels in the responsive diabetic. These more liberal criteria are also met by the biguanides in diabetics who tolerate effective doses. As the majority of mild diabetics incompletely controlled by diet alone do well with biguanides by all these standards, further careful clinical trial is justifiable.

Since moderately severe and severe diabetics, excluding the extremely labile group, less frequently tolerate effective doses of biguanide, attempted replacement of insulin with this agent does not seem indicated for those

patients doing well with insulin.

SUMMARY

1. A review is presented of earlier hypoglycemic agents, including guanidine and the compounds Synthalin A and B. These are compared with a new series of oral hypoglycemic agents known as biguanides or formamidinyliminoureas.

2. Certain parallels and differences between these compounds in terms of chemistry, metabolic effects, side-effects and possible sites of action are noted. However, the toxicity reported with guanidine and Synthalin has not occurred to date in experimental or clinical observations with the

biguanides.

3. Effects of biguanides used for varying periods of time up to 17 months were evaluated in 173 patients with all types of diabetes, including 53 juvenile-onset cases. Duration of diabetes was from newly diagnosed to 35 years.

4. Of the study group, 150 patients (88%) showed demonstrably lowered blood sugar levels, while 66 (38%) were unable to continue biguanide therapy because of gastrointestinal side-effects in the doses used.

5. Although gastrointestinal side-effects occurred frequently, they were rapidly reversible. No clinical toxicity was noted. Hepatic, renal and

hematologic studies have revealed no abnormality to date.

6. The long-term effects of the biguanides are still to be determined. However, comparison with other hypoglycemic agents suggests that, when used with certain precautions, they have clinical value in selected coöperative patients.

ACKNOWLEDGMENT

Appreciation is expressed to the U. S. Vitamin Corporation for assistance and for the biguanide compounds used.

SUMMARIO IN INTERLINGUA

Un nove serie de oral agentes hypoglycemic, cognoscite como biguanidos o formamidinyliminoureas, es comparate con sulfonylureas, insulina, e plus ancian e oralmente efficace substantias, specialmente guanidina e le compositos Synthalina A e B. Quatro analogos biguanidic es evalutate. Istos es DBI, le phenethylformamidinyliminourea, e le affinissime derivatos DBB, le amylo normal; DBTU, le iso-amylo; e DBC, le analogo methylo-benzylic (designate per alteros como PEBG,

ABG, e IABG, respectivemente). Cata un de iste substantias ha su proprie grado de efficacia in le reduction del sucro de sanguine e su proprie tendentia de producer effectos lateral. Le plus potente—in ambe respectos—es DBI, con que—usque nunc

-le plus grande numero de studios ha essite effectuate.

Le effectos metabolic de DBI resimila illos notate con guanidina o Synthalina in tanto que (1) le sucro del sanguine es reducite in animales eviscerate e in plure species post induction de diabete per alloxano, ben que a grados minus pronunciate que in animales intacte, (2) le acceptation de glucosa per le diaphragma de rattos es augmentate, sed le glucosa non es oxydate, (3) glycogeno non es formate e mesmo pote esser deplete, tanto in le hepate como etiam in musculos, (4) le responsa hyperglycemic a epinephrina e glucagon es blocate, e le mesme blocage occurre in le expectate augmento del rendimento de glucosa in le vena hepatic, e (5) acido lactic se accumula in vitro e in vivo. Viste que histos de animales previemente tractate con DBI non incorpora glucosa a C¹⁴ in proteina o lipido, iste observationes suggere que le biguanidos reduce le sucro del sanguine per augmentar le glycolyse anaerobie.

In despecto de tal similaritates metabolic, le toxicitate trovate post le uso de Synthalina ha non, usque nunc, occurrite in studios experimental o clinic con

biguanidos.

Le documentation currentemente disponibile pare indicar que DBI age super substratos in le cyclo de acido tricarboxylic per crear un bloco metabolic inter succinato e cytochromo-c. Tamen, le documentation usque nunc colligite es basate exclusivemente super experimentos acute con le uso de dosages arbitrari de DBI, de maniera que le resultatos non preclude le possibilitate de altere sitos de action pro

DBI o de effectos additional post su uso prolongate.

Effectos de biguanidos, usate durante varie periodos de usque a 17 menses, esseva evalutate in 173 patientes con omne le typos de diabete, incluse 53 casos a declaration del morbo a un etate juvenil. Le duration del diabete variava inter le extremos de recentemente diagnosticate e presente depost 35 annos. In le gruppo de patientes studiate, 150 (i.e. 88%) exhibiva demonstrabile reductiones del nivellos de sucro del sanguine, durante que 66 (i.e. 38%) non poteva continuar le therapia a biguanido a causa de adverse effectos gastrointestinal occurrente con le dosages usate. Iste effectos lateral esseva anorexia, nausea, vomito, gusto metallic, e diarrhea—in iste ordine de frequentia. Illos se provava rapidemente reversibile in omne casos post le cessation del ingestion de DBI.

Ex le 107 casos classificate como successos, 82 es currentemente tractate con biguanidos. In 57 casos, nulle insulina exogene es requirite, e in le altere 25, le

requirimento de insulina supplemental es significativemente reducite.

Nulle toxicitate esseva notate in iste experientia clinic o in le experientia de alteros. Studios hepatic, renal, e hematologic ha revelate, usque nunc, nulle anormalitate.

Le effectos del biguanidos post cursos prolongate remane incerte. Tamen, le comparation con altere agentes hypoglycemic, incluse insulina, pare indicar que biguanidos—quando usate con certe precautiones—es de valor clinic in le tractamento de certe seligite patientes de character cooperatori.

BIBLIOGRAPHY

- Underhill, F. P., and Blatherwick, N. R.: Studies in carbohydrate metabolism, J. Biol. Chem. 18: 87, 1914.
- Paton, D. N., and Findlay, L.: The parathyroids—tetania parathyreopriva: its nature, cause and relations to idiopathic tetany, Quart. J. Exper. Physiol. 10: 203, 1916.
- Watanabe, C. K.: Studies in the metabolic changes induced by administration of guanidine bases, J. Biol. Chem. 33: 253, 1918.

- Frank, E., Stern, R., and Nothmann, M.: Die Guanidin und Demethylguanidin Toxikose des Säugetier und ihre physio-pathologische Bedeutung, Ztschr. f. d. ges. exper. Med. 24: 343, 1921.
- Frank, E., Nothmann, M., and Wagner, A.: Über synthetisch dargestellte Körper mit insulinartiger Wirkung auf den normalen und diabetischen Organismus, Klin, Wchnschr. 5: 2100, 1926.
- Frank, E., Nothmann, M., and Wagner, A.: Die Synthalin Behandlung des Diabetes mellitus, Deutsche med. Wchnschr. 52: 2067 and 2107, 1926.
- Frank, E., and Wagner, A.: Über die experimentelle und klinische Wirkung des Decadekamethylendiguanids, Klin. Wchnschr. 7: 1996, 1928.
- Frank, E., and Wagner, A.: Der gegenwartige Stand der Synthalinbehandlung des Diabetes mellitus, Ergebn. d. ges. Med. 13: 451, 1929.
- Duncan, G. G.: Synthalin in treatment of diabetes mellitus, Am. J. M. Sc. 175: 196, 1928.
- Stahl, R., and Bahn, K.: Zur Kenntnis der Thrombophlebitis und Sepsis postanginosa, Deutsche med. Wchnschr. 53: 1687, 1927.
- Morawitz, P.: Unsere Erfahrungen mit Synthalin, München. med. Wchnschr. 74: 571, 1927.
- Adler, A.: Über die Nebenwirkungen des Synthalin und ihre Beseitigung, Klin. Wchnschr. 6: 493, 1927.
- Szczeklik, R.: Über die toxischen Nebenwirkungen des Synthalins, Wien. klin. Wchnschr. 40: 1075, 1927.
- Ralli, E., and Guion, C. M.: Synthalin in the treatment of diabetes, J. Lab. and Clin. Med. 14: 699, 1929.
- Bertram, F.: Zum Wirkungsmechanismus des Synthalins, Deutsches Arch. f. klin, Med. 158: 76, 1927.
- 16. Hornung, S.: Synthalin und Leberschadigung, Klin. Wchnschr. 7: 69, 1928.
- Bodo, R., and Marks, H. P.: Synthalin and carbohydrate metabolism, J. Physiol. 65: 83, 1928.
- Karr, W. G., Belk, W. P., and Petty, O. H.: The toxicity of Synthaline, J. Pharmacol. and Exper. Therap. 36: 61, 1929.
- Minot, A. S.: The mechanism of the hypoglycemia produced by guanidine and carbon tetrachloride poisoning and its relief by medication, J. Pharmacol. and Exper. Therap. 43: 295, 1931.
- 20. Creutzfeldt, W.: Alpha cell cytotoxins, Diabetes 6: 135, 1957.
- Simola, P. E.: Ueber die Wirkung des Synthalins im Tierorganismus, Ztschr. f. physiol. Chem. 168: 274, 1927.
- 22. Staub, H., and Küng, O.: Zum Synthalinmechanismus, Klin. Wchnschr. 7: 1365, 1928.
- Minot, A. S., Dodd, K., and Saunders, J. M.: Acidosis of guanidine intoxication, J. Clin. Investigation 13: 917, 1934.
- Debois, C., Defauw, J., and Hoet, J.: Sur le mécanisme d'action d'un dérive polymethyle de la guanidine, Compt. rend. Soc. de biol. 97: 1420, 1927.
- Minot, A. S., Dodd, K., and Bryan, R.: Chemical action of sodium citrate as a cause of certain transfusion reactions, Am. J. Dis. Child. 45: 32, 1933.
- Martensson, J.: Effect of guanidine and Synthalin on the citric acid metabolism, Acta med. Scandinav. 125: 82, 1946.
- Davis, J. C.: Hydropic degeneration of the alpha cells of the pancreatic islets produced by Synthalin A, J. Path. and Bact. 64: 575, 1952.
- Fodden, I. H.: Experiments with chemicals noxious to the pancreatic alpha cells, Am.
 J. Clin. Path. 23: 994 and 1002, 1952.
- Davis, J. C.: Mitoses and the protective effect of anesthetics in Synthalin nephritis, J. Path. and Bact. 67: 17, 1954.

- Hollunger, G.: Guanidines and oxidative phosphorylations, Acta pharmacol. et toxicol. 11, Supp. 1: 1, 1955.
- Allen, F. M.: Blueberry leaf extract: physiologic and clinical properties in relation to carbohydrate metabolism, J. A. M. A. 89: 1577, 1927.
- Blotner, H., and Murphy, W. P.: Effect of certain liver extracts on the blood sugar of diabetic patients, J. A. M. A. 94: 1811, 1930.
- Janbon, M., Chaptal, J., Vedel, A., and Schaap, J.: Accidents hypoglycémiques graves par un sulfamidothiazol (le VK 57 ou 2254 RP), Montpellier méd. 21-22: 441, 1942.
- Loubatières, A.: The hypoglycemic sulfonamides: history and development of the problem from 1942 to 1955, Ann. New York Acad. Sc. 71: 4, 1957.
- Franke, H., and Fuchs, J.: Ein neues antidiabetisches Prinzip, Ergebnisse klinischer Untersuchungen, Deutsche med. Wchnschr. 80: 1449, 1955.
- Marble, A., and Camerini-Dávalos, R.: Clinical experience with sulfonylurea compounds in diabetes, Ann. New York Acad. Sc. 71: 239, 1957.
- Slotta, K. H., and Tschesche, R.: Über Biguanide. II. Die Blutzucker-senkende Wirkung der Biguanide, Ber. deutsch. chem. Gesellsch. 62B: 1398–1405 (June) 1929.
- Ungar, G., Freedman, L., and Shapiro, S. L.: Pharmacological studies of a new oral hypoglycemic drug, Proc. Soc. Exper. Biol. and Med. 95: 190-192 (May) 1957.
- Pomeranze, J., Fujiy, H., and Mouratoff, G. T.: Clinical report of a new hypoglycemic agent, Proc. Soc. Exper. Biol. and Med. 95: 193-194 (May) 1957.
- Krall, L. P., and Camerini-Dávalos, R.: Early clinical evaluation of a new oral nonsulfonylurea hypoglycemic agent, Proc. Soc. Exper. Biol. and Med. 95: 345-347 (June) 1957
- Williams, R. H., Tanner, D. C., and Odell, W. D.: Hypoglycemic actions of phenethyl-, amyl-, and isoamyl-diguanide, Diabetes 7: 87-92 (Mar.-Apr.) 1958.
- Krall, L. P., and Camerini-Dávalos, R.: Clinical trials with DBI, a new nonsulfonylurea oral hypoglycemic agent, Arch. Int. Med. 102: 25-31 (July) 1958.
- 43. Odell, W. D., Tanner, D. C., Steiner, D. F., and Williams, R. H.: Phenethyl-, amyl-, and isoamyl-biguanide in the treatment of diabetes mellitus, Arch. Int. Med. 102: 520
- Nielsen, R. L., Swanson, H. E., Tanner, D. C., Williams, R. H., and O'Connell, M.: Effects on blood sugar of a new potent hypoglycemic compound, Arch. Int. Med. 101: 211, 1958.
- 45. (a) Ungar, G.: Personal communication.
 - (b) Drury, D. R., Wick, A. N., and Morita, T. N.: Lactic acid oxidation in extrahepatic tissue, Am. J. Physiol. 180: 345, 1955.
- Schmidt, L. H., Hughes, H. B., and Smith, C. C.: On the pharmacology of N₁-parachlorophenyl-N₅-isopropylbiguanide (Paludrine), J. Pharmacol. and Exper. Therap. 90: 233, 1947.
- Chen, K. K., and Anderson, R. C.: The toxicity and general pharmacology of N₁-parachlorophenyl-N₈-isopropylbiguanide, J. Pharmacol. and Exper. Therap. 91: 157, 1947.
- Goodman, L., and Gilman, A.: The pharmacological basis of therapeutics, 2nd Ed., 1955, The Macmillan Co., New York, p. 1177.
- Williams, R. H., Tyberghein, J. M., Hyde, P., and Nielsen, R. L.: Studies related to the hypoglycemic action of phenethyldiguanide, Metabolism 6: 311-319, 1957.
- (a) Tyberghein, J. M., and Williams, R. H.: Metabolic effects of phenethyldiguanide, a new hypoglycemic compound, Proc. Soc. Exper. Biol. and Med. 96: 29, 1957.
 - (b) Fajans, S. S., Moorhouse, J. A., Doorenbos, H., Louis, L. H., and Conn, J. W.: Metabolic effects of phenethylformamidinyliminourea (DBI) in normal subjects and diabetic patients, Clin, Res. 6: 252, 1958.
- 51. Tyberghein, J. M.: Unpublished data.
- Steiner, D. F., and Williams, R. H.: The effects of biguanide compounds upon respiratory enzymes, Clin. Res. 6: 55, 1958.

 Wick, A. N., Larson, E. R., and Serif, G. S.: A site of action of phenethylbiguanide: a hypoglycemic compound, J. Biol. Chem. 233: 296 (Aug.) 1958.

Harper, H. A.: Review of physiological chemistry, 5th Ed., 1955, Lange Medical Publications, Los Altos, California, p. 134.

 Horecker, B. L., and Hiatt, H. H.: Pathways of carbohydrate metabolism in normal and neoplastic cells, New England J. Med. 258: 177, 1958.

 Stetten, D., and Topper, Y. J.: The metabolism of carbohydrates, Am. J. Med. 19: 96-110 (July) 1955.

 Levine, R., Goldstein, M. S., Huddleston, B., and Klein, S. P.: Action of insulin on the "permeability" of cells to free hexoses as studied by its effect on the distribution of galactose, Am. J. Physiol. 163: 70, 1950.

 Stadie, W. C.: On the mechanism of insulin action, Am. J. Med. 19: 257-273 (Aug.) 1955.

 Renold, A. E., Hastings, A. B., Nesbett, F. B., and Ashmore, J.: Studies on carbohydrate metabolism in rat liver slices. IV. Biochemical sequence of events after insulin administration, J. Biol. Chem. 213: 135, 1955.

 Fajans, S. S., Louis, L. H., Hennes, A. R., Wajchenberg, B. L., Johnson, R. D., Gittler, D. D., Ackerman, I. P., and Conn, J. W.: Metabolic effects of sulfonylureas in normal man and in various types of diabetic patients, Ann. New York Acad. Sc. 71: 207, 1957.

 Píeiffer, E. F., Steigerwald, H., Sandritter, W., Bänder, A., Mager, A., Becker, U., and Retiene, K.: Vergleichende Untersuchungen von Morphologie und Hormongehalt des Kälberpancreas nach Sulfonylbarnstaffen (D860), Deutsche med. Wchnschr. 82: 1568, 1957.

 Renold, A. E., Martin, D. B., Boshell, B. R., and Thorn, G. W.: Studies on the site of action of the arylsulfonylureas in man, Ann. New York Acad. Sc. 71: 71, 1957.

 Pomeranze, J., and Gadek, R. J.: Clinical evaluation of a new hypoglycemic drug, in preparation.

 Weller, C., and Macaulay, A.: Preliminary observations on the use of a new hypoglycemic substance DBI, in preparation.

 Skillman, T. G., Kruger, F. A., Peterson, L. G., and Hamwi, G. J.: Clinical studies with DBI, Clin. Res. 6: 253, 1958.

66. Lenzner. A.: Personal communication.

 Camerini-Dávalos, R., Marble, A., and Root, H.: Clinical experience with orinase. A preliminary report, Metabolism 5: 904, 1956.

 Lambert, T. H.: Clinical observations with a new oral hypoglycemic agent (DBI), Clin. Res. 6: 91, 1958.

 Butterfield, J., Fry, I. K., and Holling, E.: Effect of insulin, tolbutamide and phenethyldiguanidine on peripheral glucose uptake in man, Diabetes 7: 449-454, 1958.

THE PROBLEM OF STAPHYLOCOCCAL INFEC-TIONS IN INFANTS AND CHILDREN*

By THOMAS E. SHAFFER, M.D., Columbus, Ohio

Just a few years ago it appeared that the only room for expansion for research in infectious diseases was in studies of viruses. Bacterial diseases seemed to be conquered through antimicrobial therapy and immunizations. Few persons would have predicted then that, before long, serologically identifiable strains of the commonplace Escherichia coli would be shown to be the cause of epidemic diarrhea of infants, as well as of sporadic enteritis in adults, or that the ubiquitous Staphylococcus aureus would come to occupy such a prominent position among current medical problems. Yet such is the case, as the result of developments in the last several years. The importance of bacteriology has been reaffirmed by the development of new methods for separating different groups of E. coli and staphylococci into precisely identified strains—exemplified by serologic typing of E. coli and bacteriophage typing in the case of staphylococci. These procedures have reopened the field of epidemiologic investigation in diseases that formerly could be only inadequately studied.

An additional cause for interest in "forgotten bacteria" has been the faculty of many pathogenic strains of both species to adapt to and to survive antimicrobial treatment. The reasons for this situation and its significance in the prevention and treatment of staphylococcal infections have been reviewed on several occasions, ^{5, 6, 7} and have already been discussed in this symposium.

Staphylococcal infections have become the concern of all branches of medicine because of problems of cross-infections in hospitals. They have been especially vexing for pediatricians and obstetricians, since the most impressive evidences of staphylococcal disease in recent years have been observed among young infants and postpartum women. Most physicians are familiar with the lesions of impetigo in the newborn infant. This commonplace and seemingly insignificant infection has, in recent years, been the forerunner of a number of disastrous epidemics of staphylococcal infections in maternity services.⁸⁻¹⁴

In all such epidemics in many parts of the world, a pustular skin lesion

^{*} Received for publication May 12, 1958.

From the Symposium on Staphylococcal Infections, presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 20 1058

From The Children's Hospital, Columbus, Ohio, and the Department of Pediatrics, Ohio State University College of Medicine.

Requests for reprints should be addressed to Thomas E. Shaffer, M.D., Professor of Pediatrics and Preventive Medicine, Ohio State University College of Medicine, Columbus, Ohio.

has been the most common manifestation of the infection among infants. Breast abscesses of nursing mothers, and often of the infants as well, have usually been observed. Among the infants a lesser but significant number of such serious infections as pneumonia, empyema, cellulitis, septicemia and osteomyelitis have been noted. Typically, 30% or more of the infants born during an epidemic in a maternity unit sooner or later developed evidences of infection acquired while in the hospital. Breast abscesses have occurred

in approximately 25% of the mothers who nursed their infants.

Since 1954 we have had opportunities to examine in our laboratory cultures obtained from lesions in more than 70 epidemics of staphylococcal disease in nurseries in this country, Australia, England, Hawaii, Germany and Canada. Until about five years ago, precise identification of cultures obtained from lesions due to staphylococci was impossible because of difficulty in differentiating various strains on the basis of biochemical characteristics. At the present time, however, exact characterization of single strains of *S. aureus* by means of bacteriophage typing is practicable. By this procedure, supplemented by determination of patterns of sensitivity to various antibiotics, the strains of *S. aureus* responsible for practically all of the widely separated outbreaks in maternity services occurring throughout the world during the last eight years have been demonstrated to be essentially identical.

The "epidemic" strain of S. aureus from epidemics in maternity units in recent years is lysed by phages 80 and 81 and usually by 42B, 47C, 44A and 52.16 This strain has been specified as type 80/81 by the International Reference Center, 16 but the same strain has also been designated 42B/47C/44A/52/80/81, or 52/42B/80/81, or 52/42B/81, etc., when phages distributed in the United States were used for typing. During an epidemic this strain of S. aureus has been obtained from pustular lesions of the skin, omphalitis, conjunctivitis, mastitis (in newborn infants and in nursing mothers), parotitis, pneumonia, empyema and septicemia. The organism is also found commonly in cultures from the nasal mucosa and skin of individuals who have manifest infection elsewhere, as well as of those who are not ill. The latter are usually shown to have become asymptomatic nasal carriers through contacts with infected individuals or other carriers.

Nasal or skin colonization can take place in the nursery during the first few days of an infant's life, whereas there may be no symptoms of staphylococcal infection until weeks later. This long latent period, during which asymptomatic colonization exists without manifest disease, has grave public health implications, because an antimicrobial-resistant, pathogenic strain may thus be disseminated from the hospital to the home and community. It is reasonable for physicians to assume that purulent lesions occurring in an infant less than three months of age, or in other members of his family, are almost certainly due to a strain of staphylococcus acquired in the hospital. Such infections should be considered to be potentially of great pathogenicity,

and presumably due to organisms resistant to penicillin, the tetracyclines and streptomycin. Furthermore, pyogenic infections in a family in which there is a young infant point to the probable existence of a focus of infection and potentially epidemic conditions in the nursery where the infant was born. We believe that it should be mandatory that purulent lesions of infants less than three months of age and those of postpartum mothers be reportable diseases, so that epidemiologic investigations may be made. Without such policy, hospital administrators and heads of obstetric and pediatric services might not be aware of nursery-acquired colonization and infection.

It is interesting to speculate whether the clinical manifestations of infections in infants and children are related to basic differences in susceptibility to staphylococcal infections in this age period. Studies in this field are few in number, and most of them indicate that such maternal antibodies against virulent staphylococci as can be measured in the mother's serum do pass the placenta and appear in the newborn infant. After a period of a month or two these antibodies appear to diminish, only to reappear slowly in ensuing years of childhood. 17, 18, 19, 20 It is doubtful whether these antibodies (antihemolysin, anticapsular agglutinins, antistaphylolysin) are responsible for preventing invasion by organisms harbored in the nose, but the latent period between colonization and clinical infection so often noted does have a time relationship to the drop in passively transferred antibodies.

Rammelkamp and Lebovitz ²¹ report low concentrations of coagulasereacting factors in newborn infants and young children. They postulate that this might have an effect on the localization of staphylococcal infections. However, abscesses do occur in infants, although staphylococcal septicemia and widespread pneumonia are more common in infancy and childhood

when coagulase-reacting factor is found in diminished amounts.

In epidemics in newborn nurseries the strain of *S. aureus* isolated from lesions has usually also been identified in nasal cultures of some of the personnel working in the nursery. Infants acquire the strains harbored by personnel who have prolonged contact with them. Even though infants come into intimate contact with their mothers while they are in the hospital, mothers are practically never the immediate source of staphylococci acquired by their infants. The reverse is not true, however, for we have often found that infants with clinical staphylococcal infections are capable of colonizing the skin and nasal mucosa of their mothers within a few weeks or even days.

Our studies of the manner in which newborn infants acquire S. aureus have shown that there are marked differences in the capabilities of various strains to colonize infants.²² Of 54 different strains of S. aureus isolated from more than 1,200 newborn infants, five strains accounted for 75% of the colonization, and one strain alone represented 30% of the coagulase-positive staphylococci isolated from the infants. As a rule, only one strain of S. aureus predominates in a given nursery at any one time. This situation presumably holds true for hospital wards in general, as was recently

noted by Shooter and his associates.²³ When the adult carrier of the predominating strain (almost invariably a nurse) is transferred to another nursery, in our experience the strain has disappeared only to reappear in the nursery where she was reassigned. A different strain appears and predominates in the nursery which the carrier has left. The role of the asymptomatic healthy adult carrier of staphylococci in initiating and prolonging epidemics of infections apparently depends both upon personal conduct of the carrier (coughing, sneezing, laughing, touching nose and face, etc.) and upon the potentiality of the organism to colonize infants. When the carrier is a good disseminator and the organism is a good colonizer, almost all infants acquire the organism in a short time.

Good hygienic practices in the nursery (hand washing, control of dust, the manner in which clothing and surgical dressings are handled, and deportment of personnel) are extremely important in the prevention of the dissemination of staphylococci from carrier to patient and from infected patients to other patients and personnel.²² We have demonstrated that a bactericidal liquid detergent used to cleanse the skin reduces the dispersal of staphylococci into the environment.22 It appears that this procedure should reduce cross infections from adult patients with discharging lesions. Studies of one nursery during periods when vernix was not removed from the skin by bathing showed that S. aureus could be recovered from mattresses and the crib railings, from articles commonly handled by the nurses, and from the surfaces on which lint from bedding and clothing collected. During periods when hexachlorophene bathing was practiced, fewer organisms were isolated from these same areas, and at the same time the colonization of the infants' skin and nasal mucosa was significantly reduced. It appears that when a strain of S. aureus has become established in a nursery where hexachlorophene bathing is not practiced, inhalation of airborne vernix or blanket lint contaminated with staphylococci results in increased rate of nasal and skin colonization.

Most adults who become asymptomatic carriers through contact with patients harbor coagulase-positive staphylococci for short intervals only. When contact with open, infected lesions ceases they are no longer carriers. One of the most disturbing problems in the control of staphylococcal infections in hospitals today is the disposition and treatment of hospital personnel who have become persistent carriers of pathogenic staphylococci. The advantage of detecting and controlling asymptomatic nasal carriers has been demonstrated by our experience at the University Hospital in Columbus during the last nine months. We endeavor to detect the carriers of known pathogenic strains of *S. aureus* before duties in the nursery are assumed, and periodic monthly surveys of all maternity service personnel are made. Carriers of recognized pathogenic strains are denied entry to the nurseries. Under this policy, in a nine-month period no clinical infections among infants or mothers have been noted. The detection of carriers and control

of their duty assignments are far easier to accomplish than is treatment of the carrier state. Treatment has not been satisfactory, except by preventing contact with infected individuals. However, we are continuing investigations pertinent to this problem.

Recommendations for the control of staphylococcal hospital infections when epidemic conditions prevail would include the following measures:

1. Identify the organism causing lesions and establish the common identity of strains recovered from a number of lesions.

2. Identify carriers of the pathogenic strain among personnel by culturing all purulent lesions and obtaining nasopharyngeal cultures on all personnel caring for patients. Remove carriers from intimate contact with patients.

3. Isolate all infected cases and all patients who are asymptomatic nasal carriers.

4. Appraise hospital practices to detect errors in technic which would encourage dispersion of pathogenic organisms.

5. Open another area for the admission of new patients, staffed with personnel known not to be carriers of the epidemic strain of staphylococci.

6. While carriers are being identified, when dealing with an epidemic strain of high virulence, protect infants from the moment of birth by antimicrobial therapy appropriate for the strain causing the epidemic. Newborns become hosts to bacteria in the first few days of life, and most certainly will acquire hospital-resistant strains if the proper exposure occurs. The ideal way to prevent this is to be sure that the environment and personnel do not harbor known pathogens. From a practical point of view it sometimes becomes necessary to prevent colonization by judicious use of antimicrobial protection in full therapeutic dosage until infants are discharged from hospital. Such antibiotic prophylaxis is an *emergency* procedure and should never be continued for prolonged periods, in lieu of finding carriers and improving hygienic practices.

SUMMARY

Antimicrobial-resistant, coagulase-positive strains of *S. aureus* are implicated in hospital cross-infections with increasing frequency.

Epidemics of staphylococcal infections in infants and nursing mothers have occurred in most areas of the world in recent years. The etiologic agent has almost always been a coagulase-positive strain of *S. aureus*, resistant to penicillin, the tetracyclines, streptomycin and occasionally to erythromycin. This strain is lysed by phages 80 and 81, and inconsistently by 42B, 47C, 44A and 52.

Infected individuals, as well as some who merely care for patients, become nasal and skin carriers. They are thus potentially dangerous disseminators of infection.

Infants and their mothers may be colonized in the hospital maternity service, with a delay of weeks or months before symptoms occur. During the latent period these individuals may be the source of colonization and clinical infection of others in the family. Infections in a family in which a hospital delivery has occurred within three months should be considered as hospital-acquired, and probably resistent to one or more antimicrobials.

There are differences in the capabilities of different nasal carriers to disseminate organisms into their environment. Furthermore, certain strains

of S. aureus are better colonizers than others.

The detection and reassignment of asymptomatic nasal carriers before they assume duties in a nursery for newborn infants decrease the number of infections.

SUMMARIO IN INTERLINGUA

Infectiones staphylococcal ha devenite un preoccupation de omne brancas del medicina a causa de infectiones cruciate in le hospitales. Le plus impressionante infectiones staphylococcal de acquisition nosocomial ha occurrite in departimentos de maternitate. Infantes e feminas in stato post parto ha essite afficite per epidemias in omne partes del mundo. In le majoritate del casos, il esseva possibile monstrar que le epidemias esseva causate per un racia de Staphylococcus aureus, typo bacteriophagic 80/81. Iste organismo ha essite recovrate ab lesiones de omne descriptiones e etiam ab le pelle e le mucosa nasal de patientes e de membros del personal medical durante le curso de un epidemia. Infantes acquire le organismo frequentemente in le hospital sed non deveni malade usque dies o septimanas post quitar lo. Infectiones purulente in infantes o in feminas durante le prime tres menses post parto deberea esser reportate al autoritates de hygiene public, a fin que le hospital ubi le parturition occurreva pote esser investigate pro signos additional de infection inter le patientes.

Infectiones e asymptomatic portatores nasal deberea esser identificate e lor contacto con altere patientes e membros del personal interrumpite promptemente con le

objectivo de arrestar le dissemination additional del infection.

BIBLIOGRAPHY

- Bray, J.: Isolation of antigenically homogenous strains of Bact. coli neopolitanium from summer diarrhea of infants, J. Path. and Bact. 57: 239, 1945.
- Herweg, J. C., Middelkamp, J. N., and Thornton, H. K.: Escherichia coli diarrhea, J. Pediat. 49: 629, 1956.
- Ewing, W. H.: Enteropathogenic Escherichia coli serotypes, Ann. New York Acad. Sc. 66: 61, 1956.
- Blair, J. E., and Carr, M.: Bacteriophage typing of staphylococci, J. Infect. Dis. 93: 1, 1953.
- Spink, W. W.: Staphylococcal infections and the problems of antibiotic resistant staphylococci, Arch. Int. Med. 94: 167, 1954.
- McDermott, W.: The problem of staphylococcal infection, Ann. New York Acad. Sc. 65: 58, 1956.
- Rogers, D. E.: The current problem of staphylococcal infections, Ann. Int. Med. 45: 748, 1956.
- McGuinness, F. G., and Musgrove, G. S.: An epidemic of puerperal mastitis (associated with nasopharyngeal and skin infection in the newborn), Canad. M. A. J. 61: 356, 1949.

- Isbester, C., Durie, E. B., Rountree, P. M., and Freeman, B. M.: A further study of staphylococcal infection of the newborn, M. J. Australia 2: 897, 1954.
- Hardyment, A. F.: The control of infections in the newborn, Canad. M. A. J. 70: 379, 1954.
- Shaffer, T. E., Baldwin, J. N., Rheins, M. S., and Sylvester, R. F., Jr.: Staphylococcal infections in newborn infants. I. Study of an epidemic among infants and nursing mothers, Pediatrics 18: 750, 1956.
- (a) Wysham, D. N., Mulhern, M. E., Navarre, G. C., LaVeck, G. D., Kennan, A. L., and Giedt, W. R.: Staphylococcal infections in an obstetric unit. I. Epidemiologic studies of pyoderma neonatorum, New England J. Med. 267: 295, 1957.
 - (b) Wysham, D. N., Mulhern, M. E., Navarre, G. C., LaVeck, G. D., Kennan, A. L., and Giedt, W. R.: Staphylococcal infections in an obstetric unit. II. Epidemiologic studies of puerperal mastitis, New England J. Med. 267: 304, 1957.
- Bass, J. A., Stinebring, W. R., Willard, C., and Felton, H. M.: Epidemiologic study of a hospital outbreak of micrococcic infections, J. A. M. A. 166: 731, 1958.
- Cooper, M. L., and Keller, H. M.: Severe staphylococcal infections in young children, Am. Dis. Child. 95: 245, 1958.
- Shaffer, T. E., Sylvester, R. F., Jr., Baldwin, J. N., and Rheins, M. S.: Staphylococcal infections in newborn infants. II. Report of 19 epidemics caused by an identical strain of Staphylococcus pyogenes, Am. J. Pub. Health 47: 990, 1957.
- Blair, J. E., and Carr, M.: Staphylococci in hospital-acquired infections, J. A. M. A. 166: 1192, 1958.
- Murray, J., Calman, R. M., and Lepine, A.: Transmission of staphylococcal antitoxin (antihemolysin) from mother to child, Lancet 2: 14, 1950.
- Vahlquist, B., Lagercrantz, R., and Nordbring, F.: Maternal and foetal titres of antistreptolysin and antistaphylolysin at different stages of gestation, Lancet 2: 851, 1950.
- Lichty, J. A., Jr., Katsampes, C. P., and Baum, W. S.: A study of humoral antibodies for Staphylococcus aureus in infants and their mothers, J. Pediat. 22: 549, 1943.
- Bryce, L. M., and Burnet, F. M.: Natural immunity to staphylococcal toxin, J. Path. and Bact. 35: 183, 1932.
- Rammelkamp, C. H., and Lebovitz, J. L.: The role of coagulase in staphylococcal infections, Ann. New York Acad. Sc. 65: 144, 1956.
- Baldwin, J. N., Rheins, M. S., Sylvester, R. F., Jr., and Shaffer, T. E.: Staphylococcal
 infections in newborn infants. III. Colonization of newborn infants by Staphylococcus
 pyogenes, Am. J. Dis. Child. 94: 107, 1957.
- Shooter, R. A., Smith, M. A., Griffiths, J. D., Brown, M. E. A., Williams, R. E. O., Rippon, J. E., and Jevons, M. P.: Spread of staphylococci in a surgical ward, Brit. M. J. 1: 607 (Mar. 15) 1958.
- Shaffer, T. E., Baldwin, J. N., and Wheeler, W. E.: Staphylococcal infections in nurseries, Advances Pediat. 10: 243-282, 1958.

LABORATORY-ACQUIRED TULAREMIA IN VAC-CINATED INDIVIDUALS: A REPORT OF 62 CASES * †

By THOMAS E. VAN METRE, JR., Baltimore, Maryland and PAUL J. KADULL, M.D., Frederick, Maryland

A HIGH incidence of tularemia among nonvaccinated laboratory workers has been recognized.1-12 Almost every individual who consistently works with Pasteurella tularensis eventually incurs infection; those casually exposed

may escape.8,4

The clinical features of laboratory-acquired tularemia in nonvaccinated and previously uninfected individuals have been described in detailed reports of at least 19 cases. 4-9 In general, these patients had a typhoidal illness. with moderate to severe symptoms and a relatively high incidence of chronic disability. No ulceroglandular cases have been reported. Several asymptomatic cases have been observed.

Tularemia has been reported in laboratory workers presumably immunized by prior infection. Francis 2 cited four separate ulceroglandular reinfections in a patient who had recovered from an initial severe typhoidaltype episode. In addition, Green and Eigelsbach 11 reported ulceroglandular reinfections in two patients.

Tularemia has also been reported in laboratory personnel who had re-

ceived phenolized or acetone-extracted tularemia vaccine. 1, 8, 10, 11

From 1944 to 1956, 62 cases of laboratory-acquired tularemia were observed at Fort Detrick in individuals who had received one or more courses of a phenolized and/or acetone-extracted tularemia vaccine, the composition and administration of which have been described. 1, 13, 14 A presentation of the methods of study and of some of the epidemiologic, clinical and laboratory manifestations of the disease observed in these patients follows.

DIAGNOSTIC METHODS AND CASE SELECTION

Cases were detected by intensive and continuous screening of personnel who experienced definite or potential contact with P. tularensis during their work. The development of illness in one of these individuals, or the occurrence of a break in technic resulting in possible exposure to P. tularensis,

*Received for publication January 22, 1958.
From the Biological Division, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland, and Fort Detrick, Frederick, Maryland.
Released for general publication by the U. S. Army Chemical Corps.
†Supported by a contract between the U. S. Army Chemical Corps, Fort Detrick, Frederick, Maryland, and The Johns Hopkins University.
Requests for reprints should be addressed to Thomas E. Van Metre, Jr., M.D., 1014
Saint Paul Street Raltimore 2 Maryland.

Saint Paul Street, Baltimore 2, Maryland.

inaugurated special clinical and laboratory investigations for evidence of tularemia.

Periodic subjection of personnel to determinations of *P. tularensis* agglutinin titers revealed a number of asymptomatic cases.

The following criteria were adopted for the diagnosis of tularemia:

1. Isolation of *P. tularensis* from cutaneous lesions, blood, sputum or pharyngeal washings by direct culture on glucose-cysteine blood agar or by inoculation of guinea pigs and mice.

2. One or more serum agglutinin titers of 1:1280 or greater at an interval of more than two months after vaccination was considered to be evidence of tularemia infections. Titers of such magnitude have not been observed in vaccinated individuals more than two months after vaccination.

ULCEROGLANDULAR TULAREMIA

There were nine cases of ulceroglandular disease, all initial infections occurring after at least one course of vaccine. The patients were between the ages of 20 and 39. Eight were males and one was a female. One was a chronic alcoholic; the remainder were free of concomitant disease.

Prior to onset of disease, six patients incurred minor injuries by objects contaminated with tularemia bacilli, specifically, a hypodermic needle in two instances, an autopsy tool in one, and broken glass in three. The lesion appeared at the site of trauma one day later in two cases, in two to three days in three cases, and on the eighth day in one. The eight-day incubation period occurred in a patient who had received a prophylactic course of 1 gm. of chlortetracycline daily for four days after the accident.

All patients developed initial papulo-erythematous lesions on the finger or hand; these progressed to ulceration in only three cases. A typical ulcer is shown in figure 1. Regional lymph nodes were enlarged and tender. Constitutional reactions were variable, being absent in four, characterized by malaise, chilliness and oral temperatures of 101° to 102° F. in two, and severe prostration and temperatures exceeding 103° F. in three.

Leukocyte counts were determined in eight patients within the initial five days of disease, and varied between 4,100 and 9,400. Sedimentation rates within the same interval were under 10 mm. per hour in five cases, and were 17 to 31 mm. per hour in three. *P. tularensis* was isolated from local lesions in six cases, but attempts were unsuccessful in the patient who had received a prophylactic antibiotic. Cultures were not obtained in two cases. Blood cultures were obtained in six cases and all were negative.

Seven patients received systemic antibiotic therapy, consisting of streptomycin in three cases, chlortetracycline in one case, and a combination of streptomycin and chlortetracycline in three. Response to each regimen was satisfactory, as indicated by defervescence within two days, rapid regression of the local lesions, and complete recovery within one week in three cases, two weeks in two, and four weeks in two.

Attempts to isolate *P. tularensis* from the local lesions in two cases after onset of therapy were unsuccessful in one case and successful during the first three days of therapy in another. The latter patient received only 0.5 gm. of streptomycin daily.

Antitularemia agglutinin titers rose from 1:80 or below to 1:1280 or above in four cases; from 1:40 to 1:640 in two cases; and remained at



Fig. 1. Cutaneous ulcer on dorsum of finger of a patient with ulceroglandular tularemia on the twelfth and fifteenth days of disease.

1:160 for two months in one case. In five cases, titers were measured at intervals frequent enough to indicate that the rise in antibodies began between the seventh and twenty-first days of disease, and the maximal titer was reached between the seventeenth and thirtieth days.

Two patients with small lesions unassociated with fever received no systemic antibiotic therapy. One had essentially recovered when seen on the third day of illness; the other recovered two days after institution of local treatment with streptomycin compresses. In both, agglutinin titers were 1:160 or below initially, were rising on the seventeenth to the eighteenth day of illness, and reached a peak of 1:1280 or higher between the twenty-fifth and thirty-eighth days.

TYPHOIDAL TULAREMIA

There were 43 cases of typhoidal tularemia, all initial infections occurring after at least one course of vaccine. The patients were between the ages of 20 and 49. Thirty-one were males and 12 were females. One had chronic nephritis; the others were free of concomitant disease.

Thirty-eight patients were working with the organism. Nine of these sustained known exposure to uncovered or spilled cultures, with illness appearing after two days in one, three to five days in six, and seven days in two. Five patients had not worked with the organism but had entered the tularemia laboratories.

All patients had fever and malaise, and these were the most prominent features of the illness. Thirty-three had localizing symptoms and signs suggesting respiratory tract infection; of these 33, 23 had pharyngeal irritation and/or injection, 18 had cough, four sputum, and 19 chest pain associated with coughing, breathing or swallowing.

Chest x-rays were obtained in 34 cases and revealed evidence of bronchopneumonia in 11, located in the left lower lung field in five, the left upper lung field in one, the right lower or middle lung field in four, and both the left middle and right lower lung fields in one. Blunting of the costophrenic angle on the side of the pulmonary lesion was observed twice. One patient had enlarged hilar lymph nodes on the side of the pulmonary lesion. Pulmonary cavitation was not observed. The roentgenographic appearance of a pulmonic lesion is shown in figure 2.

In the 11 cases with x-ray evidence of bronchopneumonia, physical signs of pneumonia were absent in five and inconspicuous in the remainder, consisting of râles only in five, and diminished breath sounds in one. Five patients with clear chest x-rays also had râles. Cervical lymph nodes were moderately enlarged in six cases; axillary and epitrochlear lymph nodes were enlarged in another. One patient had generalized giant urticaria on the fifth day of disease. Three had moderate hepatomegaly; four had moderate splenomegaly.

Leukocyte counts were obtained in 40 cases and were 4,000 to 4,900 in

two, 5,000 to 10,000 in 30, and 10,100 to 12,000 in eight. Erythrocyte sedimentation rates were measured in 35 cases and were less than 10 mm. per hour in six, 10 to 19 mm. per hour in six, 20 to 29 mm. per hour in five, and more than 30 mm. per hour in 18.

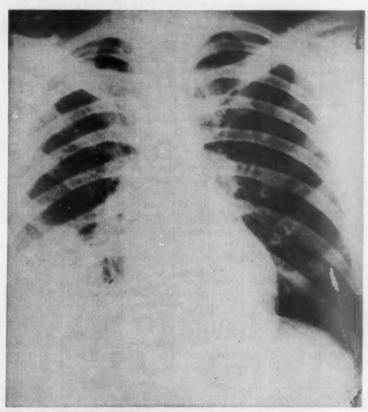


Fig. 2. Chest x-ray of patient with typhoidal tularemia, showing extensive pneumonia in right lower lung field.

P. tularensis was isolated from sputum in one case, from pharyngeal washings and blood in one case, and from blood in one case. Unsuccessful attempts were made to isolate the organism from the blood of 30 patients, and the pharynx of nine.

Antitularemia agglutinin titers rose to 1:1280 or above in all 43 patients. In 18, titers were measured at intervals frequent enough to indicate that the rise began during the first week of illness in one, in the second or third week in 14, and in the fourth week in three. In 21 of the cases there was sufficient evidence to indicate that the time of attainment of titers of 1:1280 or above

Table 1
Clinical Response of 43 Cases of Laboratory-Acquired Typhoidal Tularemia

| Patient | Antibiotic (Daily dose in grams) (Duration of therapy in days in parentheses) Strep. DihStrep. Aureo. Chloro. Terra. Achro. | | | | | | Interval in Days Retween Onset of Disease and Initiation of Therapy | Total Duration Fever in Days | Total Duration Symptoms in Days | Total Duration Pneumonia in Days (X-ray Evidence) |
|--|--|---|---|----------|--|---|--|--|---|---|
| 1 2 3 4 4 5 6 7 8 9 9 10 11 12 13 14 15 11 15 11 16 11 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 33 33 33 33 33 33 33 33 33 33 33 | 1.5 (6) 0.8 (7) 0.8 (7) 0.24 (6) 0.8 (7) 0.24 (7) 0.8 (7) 0.8 (7) 0.8 (7) 0.8 (4) 0.8 (7) 0.8 (4) 0.8 (6) 0.8 (7) 0.8 (4) 0.8 (6) 0.8 (7) 0.8 (8) 0.8 (10) 0 | 2.0 (7) 2.0 (7) 2.0 (3) 2.0 (14) 0.5 (10) 0.5 (10) 1.0 (9) 1.0 (1) | 1.0 (6) 1.5 (6) 1.20 (10) 1.0 (15) 2.0 (8) 2.0 (8) 1.0 (10) 2.0 (7) 2.0 (7) 2.0 (7) 2.0 (7) 2.0 (14) 2.0 (3) 2.0 (2) 2.0 (9) 2.0 (9) | 1.5 (10) | 0.5 (7) 1.0 (5) 3.0 (22) 2.0 (14) | 2.0 (8) 2.0 (8) 2.0 (10) 2.0 (5) | 1 3 8 8 9 9 11 1 277 80 0 180 330 1 2 4 4 5 7 8 8 12 24 ± 30 6 23 3 8 10 4 4 16 6 6 4 76 5 5 5 5 5 5 5 5 5 16 43 11 35 | 7 5 10 9 12 13 9 19 28 11 3 5 12 0 13 14 1 1 7 9 12 28 8 0 0 2 7 7 30 7 21 0 0 12 0 5 5 8 28 7 5 20 2 14 2 | 19 19 16 510+9 150 27 180+270+420 420 11 6 33 14 46 900+14 37 28 60 19 11 7 7 79 10 55 8 21 11 51 27 7 7 9 10 10 11 11 11 11 11 11 11 11 11 11 11 | 22 38 |

Note: Strep. = Streptomycin; Aureo. = Aureomycin (chlortetracycline); Chloro. = Chloromycetin (chloramphenicol); Terra. = Terramycin (oxytetracycline); DihStrep. = Dihydrostreptomycin; Achro. = Achromycin (tetracycline).

* = Strep. begun on 25th day; Chloro. begun on 55th day.

was in the first two weeks of illness in three, the third or fourth week in nine, and the fifth week or later in nine. Antibiotic therapy did not modify the agglutinin response.

Twenty-eight patients received specific antibiotic therapy within the first 30 days of illness. A variety of drugs were used, alone and in combination, including bactericidal agents such as streptomycin and dihydrostreptomycin, and bacteriostatic agents such as the tetracyclines and chloramphenicol. Choice of antibiotic, or combinations thereof, was governed by availability of the drug, sensitivity or nonsensitivity of the organism, and anticipated

TABLE 2-Response to Therapy of 43 Cases of Typhoidal Tularemia

| | _ | | | | | Ther | apy Wi | Therapy Within the First 30 Days of Illness | irst 30 | Days of I | Ilness | | | | | |
|--|---------|--------|---------------|-------------------------------|------|---------------------------|--------|---|---------|---------------------------|---------|------------------------------|--------|--|---------|------------------------------|
| | | No Ar | No Antibiotic | | Ba | Bactericidal Antibiotic* | Antibi | otic* | Bar | Bacteriostatic Antibiotic | c Antib | iotic | B | Bacteriostatic Plus Bactericidal Antibiotic | tatic P | us otic‡ |
| | П | Total | Durat | Duration after Antibiotics | Dut | Total Duration | Durat | Duration after Antibiotic | Dun | Total Duration | Durat | Duration after Antibiotic | Du | Total | Durat | Duration after Antibiotic |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | 96 | No. | % |
| Total Number of Cases | 15 | 100 | 2 | 100 | 9 | 100 | 9 | 100 | 13 | 100 | 13 | 100 | 6 | 100 | 6 | 100 |
| Duration of Fever Not present 1-5 days | 60 10 | | 7 0 | 100 | 0- | 17 | -4 | 17 | 08 | 23 | 60 NO | 38 | 00 | 00 | 02 | 0 82 |
| 6-10 days 11-20 days | | | 000 | 000 | m 71 | 33 | -00 | 100 | w rv - | 383 | 2 | 2000 | mm | 333 | 200 | 27000 |
| More than 30 days Unknown | 700 | 200 | 000 | 000 | 000 | 000 | 000 | 000 | -0- | 00% | -0- | 0000 | 000 | 300 | 000 | 000 |
| Duration of Pulmonary Consolidation Not present 1-10 days 11-20 days 21-30 days 31-40 days Unknown | 40-1000 | 800000 | ٥٥٥٥٥٠ | 000000 | 4000 | 00 00 11 00 0 | 4000 | 67 10 10 00 | 100011 | 8000000 | 100-0- | 800000 80000 | m00000 | 222003 | w0040N | £00402 |
| Duration of Symptoms Not present 1-10 days | 000 | | 000 | 643 | 0=0 | 17 | 070 | 33 | 044 | 15 | 20- | 15 00 oc | 000 | 33 | 000 | 67 |
| 21–30 days 31–60 days | 7-7 | | 000 | 000 | 1-0 | 170 | 100 | 3000 | | 3000 | -20 | 2002 | -21 | 22 | 1-0 | 1=0 |
| 61-90 days 91-149 days | -0 | | -7 | 29 | 00. | 00 | 0=0 | 170 | 000 | 000 | 000 | 000 | 000 | 000 | 000 | 000 |
| 150–560 days 1–2 years More than 2 years | 000 | 13 0 | -00 | 400 | 110 | 171 | 040 | 170 | 0 | > 00 00 | > | ⇒ ∞ ∞ | 000 | 000 | 000 | 000 |

* Bactericidal antibiotics include streptomycin and dihydrostreptomycin.

† Bacteriostatic antibiotics include tetracycline, chlortetracycline, oxytetracycline and chloramphenicol.

‡ Includes only cases receiving combined therapy for more than 24 hours. Case 26, table 1, is included with the cases receiving bacteriostatic

antibiotic therapy.

§ In every case antibiotic therapy was begun more than 30 days after onset of illness.

or evident untoward response of the individual to the drug. Response was variable, as is indicated in tables 1 and 2. The initial fever subsided promptly in most cases, and never lasted more than 30 days. Concomitantly, most symptoms disappeared and manifest lung lesions cleared. In some patients, fatigue, malaise and nervousness persisted after the subsidence of initial fever, and these symptoms were sometimes associated with low grade fever after termination of antibiotic therapy. Such symptoms, intermittently incapacitating, persisted for more than five months in four patients and did not respond to repeated courses of antibiotics. No patient treated with combined bactericidal and bacteriostatic antibiotics for three or more days within 30 days of onset of illness developed chronic disability.

Fifteen patients received no specific antibiotic therapy during the first 30 days of illness; 11 were observed before effective drugs were available. Their courses were varied (tables 1 and 2). Five individuals had symptoms for five months or longer, despite a late course of antibiotics in four instances. Seven recovered spontaneously within one month, and three responded promptly when specific antibiotic therapy was finally administered. Chronic disability was more frequent in this group than in those treated during the first month of disease.

No relationship could be established between duration of disease and age or sex of the patient, number of courses of vaccination prior to illness, and type of contact with the causative organism.

THE ASYMPTOMATIC CASES

There were 10 cases of asymptomatic tularemia, all initial infections, occurring after at least one course of vaccine. The patients were between the ages of 20 and 55, and none had concomitant disease.

Six were working with the organism, and none of these recognized an overt exposure. Four had not worked with the organism but had entered

the laboratories.

All were entirely asymptomatic. The diagnosis was established in retrospect on the basis of one or more serum agglutinin titers of at least 1:1280 observed eight or more months after the last immunization.

DISCUSSION

Analyses and observations of tularemia in nonvaccinated humans indicate that cases acquired from cultures or laboratory-infected hosts (laboratory-acquired cases) differ from those acquired from naturally-infected hosts (naturally-acquired cases). The difference is especially evidenced by the higher incidence of typhoidal cases, the absence of fatality,* and the absence

^{*} The fatal case reported by Ashburn 12 was probably acquired in the laboratory from a naturally-infected rat. 17

of ulceroglandular disease in the 20 reported cases of laboratory-acquired infection in nonvaccinated individuals. 4-9

Laboratory-acquired disease has also been observed in patients presumably immunized by prior tularemia infection. The six reported cases ^{2, 11} have all been characterized as mild ulceroglandular infections.

Laboratory-acquired tularemia has also been reported in personnel who had received phenolized or acetone-extracted vaccine.

The relatively large series of such infections gathered in this report afforded an opportunity to delineate the clinical and laboratory characteristics of tularemia in vaccinated individuals.

Ulceroglandular tularemia in the nine vaccinated individuals observed in the present series and in the two patients reported by Foshay ⁸ followed a definite clinical pattern. An initial erythematous papule, occasionally ulcerated or progressing to ulceration, appeared on the skin or mucous membranes, and, in the majority, prior trauma at the site of the lesion with objects contaminated with *P. tularensis* could be implicated. Regional lymph nodes were enlarged and tender. Fever and malaise were absent, moderate or severe. With a few exceptions, the causative organism was isolated from the primary lesion. Patients with mild infections recovered spontaneously. Patients requiring antibiotics responded promptly, and chronic residua were not observed. An associated rise in antitularemia serum agglutinins was usual but not invariable.

Typhoidal tularemia was the common type acquired by vaccinated personnel working in the laboratory. Forty-three such cases occurred at Fort Detrick, and one was reported by Foshay.⁸ Circumstantial evidence pointed to inhalation of bacterial aerosols, produced by laboratory procedures, as the mode of acquisition of this type of infection.^{1, 8, 6, 18, 16}

The clinical picture in the patients with typhoidal tularemia was non-specific and could be characterized as a "grippal syndrome," with or without evidence of upper respiratory or pulmonic involvement. In most instances the occupational history directed attention to tularemia and led to attempts to isolate the etiologic agent. These attempts were occasionally successful within the first few days of the acute illness, but more frequently they were unrewarding. Laboratory confirmation of the suspected clinical diagnosis more often depended upon the detection of a significant rise in the antitularemia agglutinin titer, which usually appeared two to four weeks after onset.

Recovery was spontaneous in patients with mild infections, and treatment of the remainder was not entirely satisfactory. Some responded promptly to antibiotic therapy, but nine of the 44 patients had disabling complaints for at least five months despite repeated courses of antibiotics. "Chronic" disabilities occurred only in those patients with a typhoidal type of infection, and was more frequent in the group that did not receive specific therapy within the first 30 days of disease. No chronic residua were observed in

TABLE 3 Laboratory-Acquired Typhoidal Tularemia: Comparison of Severity of Cases in Unvaccinated and Vaccinated Individuals

| | Unvaccinated* No Antibiotics‡ | | Vaccinated† | | | | |
|----------------------------|----------------------------------|-----|----------------------|-----|---------------------------|-----|--|
| | | | Early Antibiotics | | Late or No Antibiotics | | |
| | No. | % | No. | % | No. | 1 % | |
| Total Number of Cases | 17 | 100 | 28 | 100 | 1,5 | 100 | |
| Maximal Temperature | | | | | | | |
| 98-99.9 | 0 | 0 | 2 | 7 | 5 | 33 | |
| 100-100.9 | 0 | 0 | 2 3 7 | 11 | 5 3 3 | 20 | |
| 101-101.9 | 0 | 0 | 7 | 25 | 3 | 20 | |
| 102-102.9 | 7 | 41 | 6 | 21 | 2 | 13 | |
| 103-103.9 | 5 | 29 | 7 | 25 | 1 | 7 | |
| 104-or more | 1 | 24 | 3 | 11 | 1 | 7 | |
| Unknown | 1 | 6 | 0 | 0 | 0 | 0 | |
| Total Duration of Fever | 311 | | | | | | |
| 0-7 | 0 | 0 | 8 | 28 | 0 | 60 | |
| 8-14 | 1 | 6 | 14 | 50 | 9 2 2 2 | 13 | |
| 15-21 | · 8 2 | 47 | 2 | 7 | 2 | 13 | |
| 22-28 | 2 | 12 | 1 | 4 | 2 | 13 | |
| 29-or more | 3 | 18 | 2 | 7 | 0 | 0 | |
| Unknown | 3 | 18 | 1 | 4 | 0 | 0 | |
| Total Duration of Symptoms | | | | | | | |
| 0-7 | 0 | 0 | 2 | 7 | 3 | 20 | |
| 8-30 | 2 | 12 | 16 | 57 | 3 4 2 | 27 | |
| 31-60 | 6 | 0 | 6 | 21 | 2 | 13 | |
| 61-149 | 6 | 35 | 0 | 0 | 1 | 7 | |
| 150-or more | 8 | 47 | 4 | 14 | 5 | 33 | |
| Unknown | 1 | 6 | 0 | 0 | 0 | 0 | |
| Deaths . | 0 | 0 . | 0 | 0 | 0 | 0 | |

* Data obtained from reported cases. (4-8)

Data obtained from the cases observed at Fort Detrick. No antibiotic-treated cases in the unvaccinated group.

Treatment initiated within first 30 days of illness. Treatment initiated 30 days or more after onset of illness.

patients given three days or more of combined therapy with a bactericidal and bacteriostatic drug, such as streptomycin and chlortetracycline, before the thirtieth day of illness. Early therapy with such combinations is there-

fore advocated.

It is pertinent to question whether prior vaccination modified the course of tularemia in these patients. Inspection of the data on typhoidal tularemia in vaccinated and unvaccinated individuals (table 3) indicates that the vaccinated group tended to have lower maximal temperatures and a shorter duration of fever and symptoms. However, conclusions must be tempered with the knowledge that antibiotic therapy, causative strains of P. tularensis, and conditions of exposure differed in the two groups.

Asymptomatic infection with the virulent strains common to North America has been reported only in vaccinated individuals, and the absence of overt manifestations has been attributed to the immunity induced by the vaccine. In unvaccinated individuals, asymptomatic infection with European and Asiatic strains of *P. tularensis* of lesser virulence has occurred.^{1, 9} Detection of asymptomatic infection is obviously difficult, and it is conceivable that asymptomatic cases have been missed.

Laboratory-acquired tularemia of the ulceroglandular type has not been reported in an unvaccinated individual, and it is reasonable to conclude that the occurrence of this type of infection in vaccinated subjects is a result of some modifying effect of the vaccine.

CONCLUSIONS

1. Some of the epidemiologic, laboratory and clinical aspects of 62 cases of laboratory-acquired tularemia in vaccinated subjects are reported.

2. The evidence that vaccination modified the laboratory-acquired disease in man is discussed, and it is concluded that the efficacy of the vaccine cannot be evaluated completely.

SUMMARIO IN INTERLINGUA

Observationes de tularemia in non-vaccinate subjectos indica que le morbo, quando acquirite ab culturas o ab altere subjectos inficite al laboratorio, differe ab le morbo quando illo es acquirite ab naturalmente inficite hospites. Le differentia inter le "casos laboratorial" e le "casos natural" es specialmente apparente in le plus alte incidentia de casos typhoidal, le absentia de mortes, e le absentia de morbo ulceroglandular in le 20 reportate casos laboratorial in non-vaccinate individuos.

Casos laboratorial ha etiam essite observate in patientes supponitemente immunisate per previe infectiones per tularemia. Le sex reportate casos de iste genere esseva omnes characterisate como leve infectiones ulceroglandular.

Casos laboratorial de tularemia ha etiam occurrite in personas qui habeva recipite vaccino phenolisate o extrahite a acetona. Sexanta-duo tal casos es reportate in le presente articulo.

Nove del 62 casos esseva del typo ulceroglandular. Un papula erythematose—in certe casos ulcerate o progredente verso ulceration—appareva super le pelle o un membrana mucose. Generalmente, un trauma al sito del lesion, previemente causate per objectos contaminate con Pasteurella tularensis, poteva esser incriminate. Le nodos lymphatic regional esseva allargate e sensibile. Febre e malaise esseva absente, moderate, o sever. Con pauc exceptiones, le organismo causative esseva isolate ab le lesion primari. Patientes con leve infectiones se restabliva spontaneemente. Patientes requirente antibioticos respondeva promptemente, e nulle residuos chronic esseva observate.

Quaranta-tres casos esseva del typo typhoidal. Indicios indirecte incriminava le inhalation de aerosol bacterial, producite per manipulationes laboratorial, como modo de acquisition del morbo in iste typo de casos. Le tableau clinic esseva non-specific e poteva esser characterisate como un "syndrome grippoide," con o sin evidentia de affectiones supero-respiratori o pulmonar. Effortios a isolar le agente etiologic esseva generalmente sin successo, e le confirmation del suspicite diagnose clinic dependeva usualmente del constatation de un augmento significative in le titro de

agglutinina anti tularemia, manifeste in le majoritate del casos inter due e quatro septimanas post le declaration del morbo. Le restablimento in patientes con leve formas de infection esseva spontanee. In le caso del altere patientes, le tractamento non esseva completemente satisfactori. Certes respondeva promptemente al therapia antibiotic, sed nove del 43 habeva gravamines invalidante durante al minus cinque menses, e isto in despecto de repetite cursos de antibioticos. Le melior resultatos occurreva in patientes tractate precocemente in le curso de lor maladia con un therapia combinate a drogas bacteriocida e bacteriostatic, como per exemplo streptomycina e chlortetracyclina.

Dece casos esseva completemente asymptomatic, e le diagnose in illos se basava exclusivemente super datos serologic.

Le observationes non suffice pro demonstrar con finalitate absolute si le previe vaccination modificava le curso de tularemia in iste patientes.

BIBLIOGRAPHY

- Kadull, P. J., Reames, H. R., Coriell, L. L., and Foshay, L.: Studies of tularemia.
 V. Immunization of man, J. Immunol. 65: 425-435 (Nov.) 1950.
- 2. Francis, E.: Immunity in tularemia, Tr. A. Am. Physicians 51: 394-398, 1936.
- Foshay, L., Hesselbrook, W. H., Wittenberg, J. J., and Rodenberg, A. H.: Vaccine prophylaxis against tularemia in man, Am. J. Pub. Health 32: 1131-1145 (Oct.) 1942.
- Francis, E.: Tularemia Francis 1921: a new disease of man, Hygienic Laboratory Bulletin No. 130, 1922, Government Printing Office, Washington.
- Ledingham, J. C. G., and Fraser, F. E.: Tularemia in man from laboratory infection, Quart. J. Med. 17: 365-382 (July) 1924.
- Parker, R. R., and Spencer, R. R.: Six additional cases of laboratory infection of tularemia in man, Pub. Health Rep. 41: 1341-1355, 1926.
- Dieter, L. V.: A case of tularemia in a laboratory worker, Pub. Health Rep. 41: 1355– 1357, 1926.
- Author unknown: Psittacosis and tularemia: report of cases—infection of 2 laboratory workers in California; recovery, California and West. Med. 44: 79-80, 1936.
- Golem, S. B.: Two inapparent out of four laboratory tularemia infections, Peliklinik, Instanbul 9: 144–148, 1941.
- Howe, C., Coriell, L. L., Bookwalter, H. C., and Ellingson, H. V.: Streptomycin treatment in tularemia, J. A. M. A. 132: 195-200 (Sept. 28) 1946.
- Green, T. W., and Eigelsbach, H. T.: Immunity in tularemia. Report of two cases of proved reinfection, Arch. Int. Med. 85: 777-782 (May) 1950.
- Ashburn, L. L., and Miller, S. E.: Tularemia. A report of a laboratory infection fatal on the fifth day with early pulmonary involvement; autopsy, Arch. Path. 39: 388-392, 1945.
- Downs, C. M., Coriell, L. L., Eigelsbach, H. T., Plett, K. F., Pinchot, G. B., and Owen, B. J.: Studies on tularemia. I. Immunization of white rats, J. Immunol. 56: 229-243 (July) 1947.
- Foshay, L.: Final Report—Contract DA-18-064-CML-2394, The Chemical Corps Biological Laboratories, Camp Detrick, Md., 1 May 1953-30 April 1955.
- Johansson, K. R., and Ferris, D. H.: Photography of airborne particles during bacteriologic plating operations, J. Infect. Dis. 78: 238-252, 1956.
- Reitman, M., and Wedum, A. G.: Microbiologic safety, Pub. Health Rep. 71: 659-665 (July) 1956.
- 17. Dr. Lee Foshay: Personal communication.

RHEUMATISM AND ARTHRITIS:

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(TWELFTH RHEUMATISM REVIEW) *

Part II

By CHARLEY J. SMYTH, M.D., F.A.C.P., Denver, Colorado (Chairman, Editorial Committee), JOSEPH J. BUNIM, M.D., F.A.C.P., Bethesda, Maryland, WILLIAM S. CLARK, M.D., F.A.C.P., New York, N. Y., DARRELL C. CRAIN, M.D., F.A.C.P., Washington, D. C., DARRELL C. CRAIN, M.D., F.A.C.P., Washington, D. C.,
FELIX E. DEMARTINI, M.D., New York, N. Y.,
IVAN F. DUFF, M.D., F.A.C.P., Ann Arbor, Michigan,
EPHRAIM P. ENGLEMAN, M.D., F.A.C.P., San Francisco, California,
DONALD C. GRAHAM, M.D., F.R.C.P. (C), Toronto, Canada,
MAX M. MONTGOMERY, M.D., F.A.C.P., Chicago, Illinois,
BERNARD M. NORCROSS, M.D., F.A.C.P., Buffalo, N. Y.,
HOWARD F. POLLEY, M.D., F.A.C.P., Rochester, Minnesota,
MARIAN W. ROPES, M.D., F.A.C.P., Boston, Massachusetts, and
EDWARD F. ROSENBERG, M.D., F.A.C.P., Chicago, Illinois

CONTENTS

PART II

| "Collagen Diseases" | 34 |
|--|----|
| Psoriatic Arthritis | 11 |
| Reiter's Syndrome | |
| Neurotrophic Arthropathy: Charcot's Joints | 15 |
| Hemophilic Arthropathy 64 | 16 |
| Rheumatic (Henoch-Schönlein) Purpura 64 | 16 |
| Alkaptonuria, Ochronosis and Ochronic Arthritis | 17 |
| Palindromic Rheumatism | 17 |
| Pliarmaceutic Arthritis and Arthralgia | 18 |
| Other Types of Arthritis and Arthritic Syndromes | 18 |
| The Painful Shoulder | 19 |
| Shoulder-Hand Syndrome (Reflex Sympathetic Dystrophy) | 52 |
| Brachial Neuralgia | 53 |
| Nonarticular Rheumatism | 55 |
| Tumors of Synovial Tissue | 52 |
| Articular Disease Associated with Primary Bone Pathology | 14 |
| Congenital Defects Involving Joints | 13 |
| Structure and Function of Articular Tissues | 4 |
| Experimental Arthritis 68 | 17 |
| Spontaneous Arthritis in Animals | 19 |
| The Campaign Against Rheumatism 69 | 0 |
| | |

*Received for publication August 4, 1958.

Part I of this Review appeared in the preceding issue of this Journal.

Reprints can be obtained by sending \$1.00 to Mr. G. W. Speyer, Executive Secretary,

American Rheumatism Association, 10 Columbus Circle, New York 19, New York.

PART II

THE COLLAGEN DISEASES

The term "collagen diseases" has continued to be applied to a rather ill-defined group of diseases having as a common feature a disturbance of the connective tissue with varying degrees of vascular involvement. Such general terms as "collagen," "mesenchymal" or "connective tissue" disease serve a purpose in designating a particular systemic involvement, but should carry an implication no more specific than "renal" disease or "neurologic" disease. The fallacy of using such terms in a diagnostic sense was stressed. 886, 1844, 1741

As in previous years, etiologic mechanisms in these diseases have been discussed but the presentations have invariably lacked adequate supporting evidence. In general, most of the etiologic considerations presented can be classed in four different categories: hypersensitivity, infection, endocrine disturbance and vasomotor disturbance.¹⁵⁴⁰

A synopsis of immunobiologic reactions presented by Hagerman ⁸⁶⁴ suggested intriguing parallel characteristics in the various collagen disorders. Hypersensitivity was less attractive to other writers ^{573, 1546} as a probable mechanism for the development of these diseases, with the possible exception of polyarteritis nodosa. The role of infection in these pathologic processes has likewise been regarded as questionable because of the lack of supporting data. ^{578, 1546}

The relationship of the collagen diseases to malfunction of endocrine systems remained to be established. Selye's concept of stress and the adaptation syndromes 1863, 1865, 1866, 1867, 1868 was applied to this group of diseases. 17 The concept suggests that, in response to a nonspecific stress, the organism undergoes a series of changes constituting the "General Adaptation Syndrome," consisting of (1) an "Alarm Reaction," when the adrenal gland responds with hyperfunction; (2) a "Stage of Resistance," when the adaptation is optimal, and (3) a "Stage of Exhaustion," when the adaptation is lost. It was postulated that an imbalance in the output of glucocorticoids as compared with mineralocorticoids might be related to the development of diseases of adaptation. [A definite abnormality of endocrine function in patients with collagen disease remains to be adequately demonstrated.—Ed.]

Vasomotor disturbance is clearly a clinical feature in this group of disorders. Although this may be of etiologic significance, the pathogenetic chain of events is not at present apparent.

Vascular changes, particularly the deposition of fibrinoid material in small arteries and elsewhere, were observed to occur in varying degrees in these diseases.^{281, 320} Similar lesions have been produced experimentally in rabbits ⁷⁴⁰ after the intravenous injection of certain bacterial products. Gamble and Brunson ⁷⁴⁰ were able to produce such lesions in rabbits receiving transfusions from donor animals previously treated with meningococcal endotoxin; these studies suggested that fibrinoid, or the agent responsible for its deposition, is transported by the blood stream. [The implication is that fibrinoid deposits may not be the simple result of local tissue changes caused by direct action of a toxin. It is to be hoped that further research along these or still other lines may be fruitful in furthering our understanding of the etiology of these diseases.—Ed.]

Lansbury 1214 reviewed the relationship between various types of malignancy and the connective tissue diseases. In his careful analysis the association with

dermatomyositis was most common with reactions of the Bamberger-Marie type; disseminated lupus erythematosus and rheumatoid arthritis also appeared.

The use of electromyographic studies of patients with certain of the collagen diseases in whom myopathy was a feature offered a new method of investigation. O'Leary et al. 1556 reported that microscopic examination of muscles and myography indicated involvement of muscles in dermatomyositis, scleroderma, systemic lupus erythematosus and periarteritis nodosa. [The use of this technic deserves further investigation.—Ed.]

Systemic Lupus Erythematosus

Clinical Features. As increasing numbers of cases of systemic lupus erythematosus (SLE) have been reported, and as careful studies of prognosis such as that of Merrell and Shulman 1431 have appeared, physicians have become more aware of the prolonged course this disease may follow. A number of reviews of SLE have appeared. 552, 908, 927, 928, 1237, 1448, 1555, 1874, 2115 Familial occurrence of this disease continued to be rare enough to occasion special comment 8, 927 and case reports. 400, 435, 1387, 1706, 1710

Skin lesions were found in 30% 928 to 80% 927 of reported series. The typical erythematous macular eruption on the exposed portions of the face and the "V" of the neck has been described again. 436, 1909 Harvey et al. 227 have considered at length the skin and mucosal lesions of this disease, noting that the trunk and thighs are less often involved than are the face, chest, arms and hands. Telangiectases are often seen; some patients have transient urticaria, others pigmentation and/or vitiligo, and some, alopecia. The lesions may be pruritic. Subcutaneous nodules have been seen, as have erythematous and ulcerative mucosal lesions. 927 [More knowledge is needed regarding the similarities (if any) and differences between the nodules of SLE and rheumatoid arthritis.—Ed.] An unusual papular lesion was described in this disease. 801 The coincidence of psoriasis and lupus erythematosus has also been reported. 878

Articular manifestations appeared in 80% 1237 to 86% 927 of collected cases. The character of the joint manifestations has varied from mild transient joint pain to a condition simulating deforming rheumatoid arthritis.

Cardiac involvement, particularly pericarditis, was also reported as a common clinical manifestation which may appear in up to 50% of patients with SLE.²⁰⁶⁶ Myocardial involvement with failure also occurred, as did the endocardial lesion of Libman and Sacks. Raynaud's symptoms, occurring in 10%,⁹²⁷ signified the vasomotor instability in some patients.

Pulmonary symptoms were often the first to suggest the presence of systemic lupus erythematosus. 620, 1089, 1876 Pleurisy was the most common of the pulmonary symptoms reported; recurrent pneumonitis was not uncommon.

Convulsions and/or psychoses accounted for the largest number of neurologic manifestations in SLE. Neurologic lesions such as hemiplegia have been encountered.^{878,1896} Abnormal electroencephalographic tracings have been studied in lupus patients.¹²⁵⁸ Three cases of psychoses occurring in this disease were described,⁸⁸⁶ and observations on the role of the mechanism of depression in 14 patients were summarized.¹³⁹¹ Special attention has been given to lesions in the ocular fundus, particularly cytoid bodies,^{382, 442, 754} which are small "cotton wool" patches consisting of small groups of swollen nerve fibers, thought to result from localized deficient vascular supply.

Lymphadenopathy, splenomegaly and hepatomegaly were amply discussed. P27
Renal lesions were reported in over 60% of cases, P27 and were responsible for findings varying from simple albuminuria and hematuria to severe hypertension and uremia.

Hematologic abnormalities, such as hemolytic anemia, 814, 1419 thrombocytopenia and purpura, 849, 840, 1419 a possible circulatory anticoagulant, 2185 and a syndrome re-

sembling thrombotic thrombocytopenic purpura, 1219 have been reported.

Attention has been given to the effect of SLE on the course of pregnancy. One report of unfavorable outcome 1483 was balanced by others more optimistic. 56, 1088 A review of reported pregnancies of SLE patients 2118 revealed a maternal mortality of 20 to 60%. The presence of the L.E. factor was demonstrated for seven weeks after delivery in a child born of a mother with SLE. The factor was absent when the child reached four months. 260

Pathologic Features. The histopathology of the skin in SLE has been described as showing edema, fibrinoid deposition, hyperkeratosis and perivascular-lymphocytic infiltration.⁶¹⁹ Epithelial plugging was described as less common in SLE than in the discoid variety, while edema was usually more severe. Subcutaneous nodules have been described.¹⁵⁸⁶ Edema, cellular (lymphocytic) infiltration and vasculitis were found. In the kidney, the pathologic findings consisted of hyaline thickening of the capillary loops, hematoxylin bodies, focal necrosis and proliferative glomerulitis.¹⁹⁴¹ Renal needle biopsy was found to be helpful in making an early diagnosis ¹²⁸² and also in demonstrating serial changes in the same patients.^{636, 1492}

Pulmonary lesions found at autopsy 1070 were pleuritis, interstitial pneumonitis, atelectasis and terminal bronchopneumonia. Mucinous edema of the connective tissue in alveolar walls and in perivascular and peribronchiolar tissue was noted in a few cases. No pathognomonic lesion was identified. In the central nervous system, vascular lesions were again reported 1887 with fibrinoid

degeneration in subendothelial layers.

Unusual pathologic findings of SLE were so-called transitional skin lesions in the nail-beds ¹⁵⁷⁶ resembling those of dermatomyositis. Careful histochemical studies of fibrinoid of SLE have shown it to contain a nucleoprotein residue, which suggested a possible relationship between the hematoxylin bodies and "fibrinoid." ⁸⁵⁰

Laboratory Findings. The "L.E." Cell. Among the laboratory findings in this disease the L.E. cell test is of paramount importance, and a number of papers were devoted to it. Several authors dealt with the history and general methods of this laboratory procedure. 422, 562, 890, 1354, 1408, 1587, 1599, 2141 A variety of technics have been reported, among them the clotted blood method, resulting from the observation that the number of L.E. cells in a given preparation is increased in the presence of clotted blood; 1257, 1600 a micromethod involving marrow, 1484 and methods using blood from the finger tip, 1781 some requiring as little as one drop of blood. 1837, 1950, 1951 One report suggested the use of white cells of nonhuman species as a substrate for the test. 342 L.E. cells were produced in vivo by constricting a finger for 20 minutes and then smearing and staining blood from a finger puncture without the customary incubation. 1893 Attention was drawn to the possible misinterpretation of intracellular inclusions of cryoglobulin (cryoglobulin inclusion cells) for a positive L.E. test. 2147

Quinacrine has been shown to inhibit the L.E. factor. 559, 1280 The occurrence of L.E. cells in patients with nonlupus disease and with drug allergies (sulfonamides, arsphenamine, iodine, methylthiouracil and hydralazine) has aroused attention. 478, 948, 1440, 1408, 1716, 1876, 1928, 2194 Ogryzlo 1551 studied this test in a large variety of patients and found an occasional positive reaction in patients with other diseases,

including classic rheumatoid arthritis, scleroderma, polyarteritis nodosa, dermatomyositis, Hodgkin's disease and hemolytic anemia. Similar opinions were expressed by others. 1300 The administration of hydralazine to dogs was reported to produce renal lesions resembling those of systemic lupus erythematosus. 1300 Positive preparations were reported in cases of viral hepatitis, 1501 miliary tuberculosis 1023 and penicillin sensitivity. 1501 In the experience of Lee 1228 the test has had a high degree of specificity, no positive reactions having been found in 1,500 cases of many various diseases, including those reported above. [See section on Rheumatoid Arthritis for relationship to other connective tissue diseases.—Ed.]

Other Laboratory Findings. Radiologic findings of focal pulmonary patches of ill-defined infiltration and small plaques horizontal to the diaphragm 828 were described. Circulating anticoagulants, 728, 1229 abnormal liver function tests, 1159 elevated serum hexosamine, 200 and biologic false-positive serologic tests for syphilis 1474 were reported. A general review of the laboratory tests found in SLE appeared. 1818

Etiology and Pathogenesis. Although interest in hypersensitivity and autoantibodies 762, 1877 continued, convincing evidence regarding etiology was not cited.

Treatment. As was pointed out by Harvey et al. 927 general measures were of prime consideration. Limitation of activity, salicylates when needed, avoidance of antibiotics except when definitely indicated (SLE patients were prone to manifest allergic reactions), and digitalis for cardiac complications were all important measures. In general, fever, arthritis and/or arthralgia and skin and mucous membrane lesions cleared rapidly in most patients during steroid administration, 180, 927, 1955, 1956 although renal and cardiac changes were less likely to yield. Repeated admonitions regarding side-effects and the necessity for administering the lowest possible dose of steroids appeared. 721, 2170 The newer steroids, prednisone and prednisolone, have proved effective in suppressing clinical manifestations of SLE. 221, 540, 541 As with cortisone, renal and cardiac disturbances were less likely to respond. Psychosis complicated management of SLE patients receiving cortisone and ACTH. 1217 [Psychotic states occur in this disease without hormone therapy as well as during such therapy, and may improve on such therapy.-Ed.] The influence of ACTH and cortisone on the incidence of infections in disseminated lupus erythematosus was investigated. 142 The 21 patients who received hormone therapy were observed for 209 months on therapy and for 275 months without such medications. It was concluded that therapeutic doses of ACTH and cortisone did not influence the incidence of infections in these patients. [These results are not in accord with the clinical impressions of some. One of us (M. W. R.) considers infections as the complication she fears most.—Ed.]

The antimalarial compounds were employed; ⁵⁶¹, ¹⁵⁰⁰, ²⁰⁸² Atabrine was less effective in more acute forms of the disease. ⁵⁶¹ Chloroquine was less likely to induce gastrointestinal symptoms and, unlike Atabrine, did not cause yellowing of the skin. Chloroquine promoted improvement in over half of the patients treated. [One of us (I. F. D.) considers the long-term administration of hydroxychloroquine to be beneficial in SLE. Further careful study of the place of this preparation in the treatment of this disease is certainly warranted.—Ed.] Nitrogen mustard was said to be effective in the control of the nephrotic phase of SLE. ⁵⁶⁰

POLYARTERITIS NODOSA

Clinical Features. Polyarteritis nodosa (PAN) occurred in the very young as well as in adults; several case reports documented its appearance in

infants from four to nine months of age. 625, 1047, 1260 In general, the disease appeared more frequently in males (incidence 4:1). 1541

The concept persisted that PAN was an inflammatory disease involving multiple small and medium sized arteries, resulting in a clinical syndrome of fever, tachycardia, weakness, hypertension, and pain in the muscles, chest and abdomen, with frequent involvement of the gastrointestinal tract, peripheral nerves, lungs, kidneys and skin.^{192, 559, 558, 947, 1270, 1304, 1454, 1491, 1541, 1796} Patients often presented themselves for diagnosis of a fever of unknown origin, ¹⁴⁵⁴ or with an acute "surgical abdomen." ^{589, 1484}

Gastrointestinal symptoms were found in 62% of 175 cases ¹⁸⁴¹ and in 45% of 607 cases; ¹⁴⁹¹ abdominal pain, nausea and vomiting were common manifestations. Intestinal wall involvement simulated enteritis, with frequent loose stools ¹²²⁴ or intestinal obstruction. ¹³⁰⁵ Infarction of the small intestine ¹⁶⁷⁸ and intussusception ²²⁹³ have resulted from lesions of this disease. Hepatic infarction and aneurysms ^{778, 1491} occurred, and hemorrhagic infarction of the pancreas was observed. ¹⁵⁴¹ Symptoms could suggest peptic ulceration, and occult blood was present in the feces. Intraperitoneal hemorrhage and perforation of the gastrointestinal tract have occurred. ¹³⁰⁴

Peripheral neuritis occurred in 42% of 607 cases 1491 and in 54% of 175 cases. Paresthesias occurred in a random distribution, but the pattern was usually symmetric. 933, 934 Later, muscle atrophy of disuse has developed. Central nervous system symptoms such as convulsions, psychiatric disturbance, vertigo and/or ascending paralysis were reported. 1491

Pulmonary symptoms were encountered in from 36% ¹⁴⁹¹ to 47% ¹⁸⁴¹ of reported series; infarction, pleurisy and pneumonitis accounted for most of the symptoms ⁵⁴⁸ of cough, hemoptysis, ⁶⁰⁹ dyspnea and chest pain noted by the patients. Asthmatic complaints, ¹⁸⁰⁴ upper respiratory tract involvement with sinusitis, and granulomatous lesions of the nose were recorded. ¹⁸⁸⁸ The most common cardiac symptom was tachycardia, found in 45% of 607 cases collected by Mowrey and Lundberg. ¹⁴⁹¹ Myocardial infarction was reported, but angina was rare. Cardiac enlargement and congestive failure were more common manifestations. Hypertension was found in 58% of these patients.

Petechial and other skin rashes were found in 35% of the 175 cases collected by the Nuzums, 1541 and subcutaneous nodules in 16%. Skin lesions included (1) small subcutaneous nodules, occurring in crops lasting a few days to many months, (2) areas of ecchymosis and cutaneous gangrene, (3) acute erythematous, urticarial or purpuric skin rashes, (4) livedo reticularis, generalized purple arborescent marking of the skin, and (5) multiple ulcerative lesions. 1820

Renal lesions were considered to be responsible for the hypertension so common in PAN. Uremia was a terminal event in 26% of the 175 cases of the Nuzums. 1541 Edema may result from the kidney lesion. The nephrotic syndrome was reported secondary to bilateral renal vein thrombosis. 1488 Renal tubular failure was also seen as secondary to multiple renal infarcts and glomerular disease. 481 Involvement of joints was suggested by the frequent polyarticular pain and, in some instances, inflammation. The association of the full syndrome of rheumatoid arthritis and PAN was reported by Ball. 91 [Synovitis rarely occurs in PAN but, when present, may simulate rheumatoid arthritis.— Ed.]

Wegener's granulomatosis was considered to be a unique respiratory-renal subtype of polyarteritis nodosa. Seven new cases of this syndrome were reported, and its differentiation from other types of arteritis was discussed. 653, 794

Pathologic Features. The essential pathologic lesion of PAN has been described many times as a widespread segmental arteritis of small and medium sized arteries. In early lesions, mural degeneration and infiltration of eosinophils and polymorphonuclear cells occurred; later, fibroblastic proliferation with aneurysmal dilatation or vascular narrowing and occlusion with thrombus formation and reorganization was present. Areas of hemorrhage from the aneurysmal dilatation, and infarction from the proliferative lesions in multiple organs, accounted for most of the protean manifestations of PAN. The pathologic findings in various organ systems have been well reviewed by the Nuzums; ¹⁸⁴¹ 175 cases revealed renal lesions in 85%, cardiac in 76%, pulmonary in 24% and cutaneous in 20%. Hepatic involvement ¹⁴⁹¹ consisted of aneurysm and rupture, infarction, interstitial hepatitis or cirrhosis. Granulomatous disease of the nose has been reported. ¹⁴⁵⁹ Six cases of necrotizing pulmonary angiitis were reported in which the lesions were associated with pulmonary hypertension. ²⁵⁵ Special involvement of the brain ¹⁸⁰⁸ was also described.

Laboratory Findings. No specific laboratory tests were available for PAN. In general, patients were found to have elevated erythrocyte sedimentation rates, and often showed leukocytosis (10,000 to 25,000 per cubic millimeter)¹⁵⁴¹ and eosinophilia. Albuminuria, occasional red cells and casts in the urine were found in patients with renal involvement. The stool often contained blood. Cryoglobulinemia was noted.⁸⁰⁷ Radiologic changes in the lungs consisting of parenchymal infiltration, sometimes transient, were reported.^{548, 2084}

Etiology and Pathogenesis. The etiology of PAN remained unknown. Older ideas of bacterial or viral etiology, degenerative disease, drug hypersensitivity and "disease of adaptation" were dutifully restated in most reviews. The PAN syndrome did not result from hypertension, 1541 but 10 cases of PAN associated with malignant hypertension were presented. Additional cases of PAN following penicillin administration 465, 2041 and iodides 1699 were reported. An anti-aortic antigen factor, demonstrated in the serum of two patients with PAN and anaphylactoid purpura, suggested an immunologic factor in the disease of these patients. 1996

Experimental studies in rats were reported, with the production of PAN with follicle-stimulating hormone (FSH) ¹⁶¹⁶ with NaCl in hypertensive rats, ¹⁶⁷⁹ and the prevention of PAN in hypertensive rats by means of sodium restriction and the rice diet, ¹¹⁸⁰ A reduction of the vascular lesions in hypertensive rats (induced by DOCA and NaCl feeding) was accomplished by hypophysectomy. ¹⁸⁰⁹

Treatment. Treatment in general remained symptomatic, but many encouraging reports of the use of cortisone 964, 1339, 1541, 1969 or ACTH combined with cortisone were noted. 942 Special problems in skin grafting of ulcerated areas were discussed. 964

DERMATOMYOSITIS

Clinical Features. Dermatomyositis was still described as an uncommon, loosely defined systemic disease, most often manifested by the skin and muscle changes, but occasionally presenting with vascular and degenerative lesions in other organ systems. Little has recently appeared to improve our understanding of this disease process. Several reports of single cases have been published.⁰⁸⁷

1462, 1988 One collection of 40 cases in children 1744 presented the usual symptomatology in organized fashion. General symptoms of fever, malaise and tachycardia were often encountered. The muscles were often stiff and painful, and weakness was a frequent complaint. Muscles later showed atrophy; contractures of joints at times appeared. Dysphagia and dyspnea reflected involvement of other muscle groups. Occasionally inflammatory joint disease was seen. Skin lesions were varied; periorbital edema with bluish discoloration of the skin was frequently described. Urticaria, erythema, purpura and bullous formations, as well as ulcerations and calcinosis, were described. Alopecia rarely appeared. The course was more severe in children in this series than it usually is in adults: only two of 40 cases escaped crippling.

A special point has been made of the association between malignancy and dermatomyositis, Caldwell 817 having reported three cases and Dowling 558 a collection of 30 cases. In many, the malignancy clearly preceded the onset of dermatomyositis, which in some cases improved with surgical correction of the malignancy. A variety of tumors were recorded in this peculiar association.

Pathology. The pathology of dermatomyositis was described generally 2084 as muscle fiber fragmentation, interfibrillar edema, and cellular infiltration with lymphocytes and occasionally plasma cells. "Muscle giant cells" (multinucleated muscle cells) were described. Arteriole narrowing and thrombus formation were also mentioned. In the skin, thinning of the various layers has been seen, as has vasculitis. Mendeloff 1824 has reported focal microscopic lesions in the myocardium, some with interstitial edema and others with fulminating vasculitis and myocardial degeneration and round cell infiltration.

Laboratory Findings. In one study,²⁰⁵⁴ mild anemia, leukocytosis, an increased erythrocyte sedimentation rate, albuminuria and casts in the urine were noted; creatinuria also was a common finding. [The occurrence of renal involvement as part of this disease has not been proved.—Ed.]

Etiology. No new ideas were presented.

Treatment. Treatment remained symptomatic. Most observers ^{334, 1744, 1965, 2054,} ²²⁴⁰ expressed guarded optimism regarding the use of steroids in suppressing the more acute manifestations of the disease. [We agree.—Ed.]

SCLERODERMA

Clinical Features. An increased interest and availability of improved approaches to the investigation of the clinical manifestations of scleroderma were evidenced in several reviews. Sold, 1238, 1635 In 150 cases the range in age war from three to 65 years, and the female to male incidence, 2.7:1. The span of disease extended from eight months to over 30 years.

The skin was universally involved. Initially there was swelling, with later tightening and atrophy. Pigmentation and vitiligo were frequent. Hands, face, chest, forearms, feet and legs were involved. Fingertip ulcers, paronychiae and Raynaud's phenomena were often seen, and, in later cases, calcinosis at times was noted. Gastrointestinal tract involvement occurred in 97% of one series of 31 patients, 1635 dysphagia having been an early symptom. Epigastric pain, diarrhea and constipation occurred. Special radiologic study of the small bowel was reported in six patients, 5 in whom marked dilatation was found in some areas, with decreased peristalsis. The mucosal pattern also appeared to be abnormal in a few cases.

Pulmonary involvement was stated to be severe at times, and could present as chronic bronchitis. Pulmonary fibrosis was often found, 1862 and pulmonary hypertension occurred. Pulmonary symptoms might have been due to alveolar respiratory impairment. In some cases, ventilatory difficulty resulted from tightening of the skin of the thorax. Cardiac involvement was reported; 115, 806 electrocardiographic changes suggested mild conduction defects. In Defects in the vascular supply 996 were found in some patients. Renal impairment in scleroderma was associated with successive hypertension, uremia and death. In Joint symptoms occurred in 97%. In A case of scleroderma associated with hemolytic anemia was reported.

Pathologic Features. Pathologically, the skin showed atrophy of dermal appendages, sclerosis of the subdermal tissues, and areas of increased pigmentation in the basal layer and scattered areas of intimal thickening in small arteries and veins. Calcium plaques were rarely observed. 1288, 1635 Ulcers were found at almost all levels of the gastrointestinal tract; thickening of the intestinal wall was also found. In the lungs, diffuse fibrosis and pulmonary vasculitis were observed. Cystic changes also were recorded. In the heart, pericardial lesions were found in some cases. Myocardial fibrosis was often noted. Renal involvement with cortical infarctions and arteriolar changes was reported. 108

Laboratory Findings. No new diagnostic laboratory tests have become available. The erythrocyte sedimentation rate was sometimes elevated. Urinary changes might signal the possible development of serious renal involvement. Radiography proved useful in assessing the degree of gastrointestinal disturbance, 546 as well as pulmonary

fibrosis, cardiac enla gement and articular changes.248

Etiology. No new data appeared.

Treatment. Although no specific treatment became available, use of steroids was moderately successful, according to most observers. 1238, 2294 [There is little or no effect in many cases.—Ed.] Improvement in blood flow 852 and in skin lesions 1810 was attributed to administration of cortisone. Isolated reports of successful treatment by chelation 1150 and by intravenous 2% procaine 144 have appeared. [The hormone relaxin, an extract of the ovaries of pregnant sows, has been reported to be beneficial in healing chronic ulcers and in loosening the skin in patients with scleroderma. 247, 1789—Ed.]

PSORIATIC ARTHRITIS

"Psoriasis arthropathica" was observed in association with rheumatoid arthritis, rheumatoid spondylitis and Still's disease in approximately 8% of the cases. 436 The higher incidence of psoriasis in arthritic subjects was again noted; the incidence of psoriasis in rheumatoid arthritis was 2.7%, but it occurred in only 0.7% of nonarthritics. 1783

Clinical Features. It was postulated that psoriatic arthritis was a clinical entity distinct from rheumatoid arthritis. Separation of psoriatic arthritis into two types was suggested. The term "psoriasis arthropathica" was advised for cases characterized by involvement of the nails and distal joints of fingers and toes associated with x-ray findings of destruction of the joint surfaces and increased bone density producing the "pencil in cup" deformity. Involvement of large joints was not considered to be rare in patients exhibiting such findings. [The relationship of the two types is not yet known.—Ed.] Skin lesions antedated

the arthritis, occurred at the same time, or followed the joint involvement.⁴⁸⁶ The typical destructive radiologic findings were frequently not found when the dermal psoriasis was paramount.¹⁷⁵³ In psoriatic arthritis the blood count, erythrocyte sedimentation rate, serum protein content and electrophoretic patterns were characteristic of those of any group of patients with rheumatoid arthritis.

The nail changes in psoriasis could be recognized at first sight 1767 by the characteristic detachment of the nail from the nail-bed, the mixture of flat, spoon-shaped, crooked, splintered nails, the debris-filled nail beds, and the holes in the nails. The terminal interphalangeal joint involvement subjacent to this characteristic fingernail distinguished psoriatic arthritis.

Treatment. Adrenal corticosteroids influenced both the arthritis and the psoriasis, but unresponsiveness of the skin lesions to the hormones was also demonstrated. Usually, high doses of steroids were necessary to control the psoriasis, and relapses followed withdrawal.³⁸⁴ In another report the use of large doses of cortisone in the treatment of skin manifestations was found to be effective.¹²⁶⁷ Improvement was maintained with reduction of doses, but relapse occurred sometimes during the reduction period. [The superiority of triamcinolone has recently been reported.¹⁸⁸²—Ed.] Phenylbutazone was effective in the management of the arthritis but not of the psoriasis.²¹⁴² In one series of 12 cases of psoriasis associated with rheumatoid arthritis the average dose used was 400 mg. daily for from four to seven days, followed by a maintenance dose of 200 mg. daily.²¹⁴²

REITER'S SYNDROME

Several reviews and reports on Reiter's syndrome appeared. 131, 283, 816, 706, 795, 802, 891, 2186 In spite of widely different views as to its definition, etiology and mode of transmission, it was most widely known as a syndrome of unknown cause characterized by the presence of the triad of nongonococcal urethritis, conjunctivitis and arthritis. 283, 2186 Harkness recognized two types of this syndrome. The endemic or venereal type, rarely seen in women, occurred most frequently, followed sexual exposure, and was usually first manifested by a nongonococcal urethritis. The epidemic or dysenteric type occurred during convalescence from dysentery, was not a venereal infection, and was reported in a number of women. Urethritis was usually seen in this type also, but the order of appearance of members of the triad was not so characteristic as in the venereal type. A gonococcal urethritis associated with the urethritis of Reiter's syndrome was not unusual.283,891 [Recognition of coincidental gonococcal urethritis and Reiter's syndrome has simplified the diagnostic problem of certain patients with arthritis following urethritis. The development of typical Reiter's syndrome following adequate penicillin therapy of proved gonococcal urethritis has not been unusual. Reiter's syndrome occurs more frequently than does gonococcal arthritis. This term should not be used as descriptive of a definite group, and even mouth lesions do not establish the diagnosis if the triad is not present. Strict adherence to the diagnostic triad will avoid confusion.—Ed.]

Clinical Data. Up to a third of reported patients had diarrhea as the first evidence of the disease. [This seems high to us.—Ed.] Urethritis, conjunctivitis and arthritis most frequently appeared, in that order and within a period of from one to four or five weeks. Any one of the triad has been known to initiate the

syndrome, and in some patients urethritis or conjunctivitis was not noticed. At the onset, fever occurred in practically all patients. The usual episode lasted from two to six months, and during this period there were sometimes exacerbations of urethritis, conjunctivitis or arthritis. Recurrences have been frequent. Less common findings included periositis of the calcaneus with subcalcaneal spurs and plantar fasciitis, periositis with marginal osteophyte formation, 891 tendinitis, myositis and bursitis. Pleurisy, myocarditis and pericarditis, and the development of ankylosing spondylitis, were also reported. 283, 2186 The prognosis as regards life was reported as good; no fatalities have been reported. 288

Articular Involvement. Acute polyarthritis dominated the clinical picture, although occasionally a single joint was involved. At the onset the acutely affected joints were warm, swollen, painful and tender. Most patients had no residual evidences of joint disease after the attack subsided. A few had joints involved as long as 18 months, and in rare instances, after repeated attacks, a patient was observed to have evidence of chronic active joint disease.^{288, 891, 2186} [Such cases may be indistinguishable from rheumatoid arthritis or rheumatoid spondylitis.—Ed.] Roentgenograms taken early in the course seldom showed more than periarticular thickening and slight subchondral bone atrophy. In patients with severe joint manifestations, osteoporosis was marked. The radiographic changes generally were reversible, but sacro-iliac changes were observed to be progressive.^{285, 891, 2186}

Genitourinary Involvement. The urethritis of Reiter's syndrome was occasionally associated with a gonococcal urethritis.^{283,891} The latter was readily cured by penicillin therapy. The clinical findings varied from a mild, almost asymptomatic, serous discharge of a day's duration to a purulent bloody discharge. Epididymitis was not reported. An abacterial pyuria was found in some patients who had not noticed a preceding urethritis.^{802,2186} [Prostatitis, cystitis and pyelonephritis also occur in Reiter's syndrome.—Ed.]

Ophthalmic Involvement. Conjunctivitis was by far the most common eye finding, and was occasionally associated with keratitis or iritis. In a few patients, ocular involvement was severe and of months' duration, but recovery without loss of vision was the rule. Recurrent episodes of conjunctivitis alone, either preceding or following Reiter's syndrome, have occurred ^{795, 2186} One patient with Reiter's syndrome was reported to have had, in a seven-year period, eight episodes of conjunctivitis, complicated by keratitis four times and by iritis six times, with an associated central retinitis four times. Recovery was complete except for a minute paracentral scotoma for red.¹⁸⁷⁹

Mucocutaneous Involvement. Mucous membrane lesions of the mouth, pharynx and genitalia, with skin lesions conforming to the descriptions of keratodermia blennorrhagica, were again reported. The balanitis lesions in the uncircumcised were painless, superficial, moist erosions on the corona and perimeatal region. In circumcised males the balanitis often appeared as crusted hyperkeratotic lesions. The skin lesions first appeared as erythematous macules, which later became waxy cones. These lesions increased in number, coalesced and became firm, thick, hyperkeratotic crusts or plaques. Some finger and toe nails became opaque and brittle. Subungual accumulations of keratotic material resulted in temporary loss of nails. 131, 2186 [The changes in nails of the hands and feet resemble those in psoriatic arthritis, and the skin lesions often cannot be distinguished from pustular psoriasis, even histologically.—Ed.]

Pathology. Biopsy examination of joints showed an edematous, markedly congested and hemorrhagic synovialis. The blood vessels were dilated, and there was polymorphonuclear leukocytic infiltration on microscopic examination. Later in the course, hypertrophy and hyperplasia of the synovial cells, with

lymphocytic infiltration and perivascular connective tissue cell proliferation, were also seen. [These changes also suggest the close relationship of Reiter's syndrome with rheumatoid arthritis.—Ed.] The mucous membrane and skin lesions showed parakeratosis, acanthosis, and elongation and hypertrophy of the rete pegs. Degeneration of the epithelial cells and accumulations of polymorphonuclear leukocytes gave rise to pustular microabscesses. The papillary layer of the corium was infiltrated by lymphocytes, plasma cells and polymorphonuclear leukocytes. Similar changes were found on examination of the oral mucous membrane lesions.²¹⁸⁶

Laboratory Data. Nonspecific findings of leukocytosis, increased sedimentation rate, pyuria and prostatic and urethral smears showing pus cells were again reported. Pleuropneumonia-like organisms were cultured from urethral secretions in some cases. Serologic reactions between these organisms and the sera of patients with Reiter's syndrome have been negative. ²¹⁸⁶ However, it was of interest that a woman who did not have Reiter's syndrome but had a postpartum infection due to the pleuropneumonia-like organisms developed specific antibodies and a positive complement fixation test. ²⁰¹⁹ Urethral and conjunctival scrapings have shown the pleomorphic inclusion bodies of pleuropneumonia-like organisms and, rarely, the elementary bodies of the virus of inclusion conjunctivitis. ⁸⁹¹ Synovial fluid cell counts ranged from 3,000 to 55,000 per cubic millimeter, with an average of 65% polymorphonuclear leukocytes. Glucose values of synovial fluids were decreased in some instances, and the content and characteristics of mucin were sometimes altered. ²¹⁸⁶

Etiology. The etiology remained obscure. The gonococcus and the dysentery bacilli were no longer considered to be satisfactory etiologic possibilities. Evidence that Reiter's syndrome was an allergic reaction was not found, and it seemed improbable that it is a variant of rheumatoid arthritis. 283 [Some of us think that it may be.-Ed.1 Pleuropneumonia-like organisms (L-organisms) were again considered by some to be the agents most likely responsible, but accurate evaluation could not be made until more is known of these organisms. 288, 316, 891, 915, 2186 These have been recovered from the genitourinary tracts of patients with Reiter's syndrome, but have also been cultured from the genitourinary tracts of normal males. Recent studies have shown that pleuropneumonia-like organisms represented unusual growth forms of commonly occurring bacteria, and that they also reproduced in this form, which differed from the parent organism. They reverted to their normal bacillary form in some instances. However, the parent organisms of strains isolated from patients with Reiter's syndrome were not identified. Two strains isolated from the synovial fluid of patients with Reiter's syndrome could not be carried in subcultures. Many commonly occurring bacteria exposed to penicillin in vitro underwent transformation to this virus-like form, and then reverted to their usual bacillary form when penicillin was eliminated.²¹⁸⁶ Pleuropneumonia-like organisms were also isolated from the large intestine of normal individuals.891 [The relationship of an infection by pleuropneumonia-like organisms to Reiter's syndrome remains unproved. See Experimental Arthritis section.-Ed.]

A virus was possibly a responsible etiologic agent.^{288, 891} It was suggested that antibiotics played a role in the growth of organisms in vivo and brought about a fixed tissue antigen-antibody reaction resulting in the syndrome.⁸¹⁶ [There is little evidence that this is the case.—Ed.] Reiter's syndrome was considered to be coincidental to injury in one case, while in another it was concluded by a Workmen's Compensation Board that trauma to an ankle had acted as the precipitating factor.¹⁸⁹⁷

Treatment. The value of any therapeutic agent was difficult to determine because of the usually self-limited nature of the syndrome. 1715, 2186 Bed-rest. passive motion of affected joints, splints for painful joints, massage, salicylates and other analgesics were recommended. Arsenicals, foreign protein injections, fever therapy, gold salts, sulfonamides and penicillin were used without benefit and were not recommended. 288, 891, 2186 [Fever therapy is still favored by some of us.-Ed.] Tetracycline hydrochloride, streptomycin and other antibiotics were used for treatment of the urethritis, but this usually subsided in a week or so, with or without such therapy. 891, 2186 The ocular manifestations responded promptly to ACTH or cortisone therapy. 795, 1879 These substances also controlled the joint symptoms temporarily, 283, 478, 891, 2186 although response of a 62 year old woman to cortisone therapy was reported as poor. 1718 The duration of an episode of Reiter's syndrome was not shortened by the use of ACTH or cortisone. A high dosage schedule was necessary, and treatment over a prolonged period was needed in the severe form of the disease. The steroids were withdrawn gradually, but the dosage was increased again if needed to control pain. These agents were not needed for control of milder forms of the disease. While not curative, ACTH and cortisone represented the best available symptomatic therapy for patients with the severe form of Reiter's syndrome. 706, 2186 Symptomatic benefit is recognized, but the value of any therapeutic measure in this usually self-limited disease is difficult to ascertain.—Ed.]

NEUROTROPHIC ARTHROPATHY: CHARCOT'S JOINTS

Whereas formerly neuropathic arthropathy of the lower extremities was usually due to syphilis (tabes dorsalis), diabetes mellitus now showed the higher incidence. In the upper extremity, syringomyelia with its accompanying lesions in the cervical cord was responsible for progressive joint destruction.

Clinical Data. Eight patients with clinical evidence of tabes dorsalis seen during a two-year period in one hospital were found to have radiographic evidence of Charcot's spine. The disproportion between the severity of the radiographic changes and the discomfort of the patient was significant. There was usually a kyphotic deformity with lateral curvature and rotation due to compression of the vertebral body in the lower dorsal and lumbar spine, with both proliferative and destructive changes.³²⁵

Diabetic neuropathic arthropathy of the foot was recognized with increasing frequency; 17 cases were observed over a five-year period in one hospital.¹⁴⁵² The joints usually involved were the interphalangeals, metatarsophalangeals and tarsals.¹²⁷⁸ Although the exact modus operandi was not apparent, poor control of the diabetic process was considered to be an important factor. Nerve

damage, with involvement of the peripheral nerves, the nerve roots and the posterior column, was the most consistent finding; 1278 nonmyelinated nerve fibers appeared to be involved early, and predisposed to excessive trauma and "lowered tissue resistance." 1380 In a radiologic study in which bone changes were observed in 13 patients, the classic features of a Charcot joint were not seen in any cases. An alternative explanation of these joint changes was that the lesions were caused by a low grade inflammatory lesion resulting in bone and joint destruction. 481

Treatment consisted of adequate control of the diabetes plus immobilization of the affected joints. Surgical procedures which may be necessary for infected joints included incision and drainage, amputation and exostosectomy. The intramedullary nail was not a satisfactory method of producing an arthrodesis in three patients with Charcot's knee joints. In two patients, fracture of the femur occurred through the window used for insertion of the nail; in the other, the nail broke at the joint line when satisfactory fusion did not result. Surgical fusion of an advanced Charcot's joint remains very difficult, and usually impossible.—Ed.]

HEMOPHILIC ARTHROPATHY

Twelve cases of hemophilic arthritis occurring in six families were found to show a high incidence of bone and joint changes radiographically. Three stages of involvement were recognized: an early stage incident to acute hemarthrosis, with swelling, tenderness and local heat; a moderately advanced stage from repeated hemorrhages into the joint, showing hypertrophy of the synovial membrane, thickening of periarticular tissues, and erosions of articular surfaces; and an advanced stage, with cartilaginous destruction, osteophyte formation and subluxation. Hemorrhages into smaller joints were more likely to produce destruction than those into larger joints. This needs to be confirmed.—Ed.]

Christmas Disease. Closely related to hemophilia, and not distinguished from it symptomatically, is a recently separated condition. 14, 170, 287, 1711 Patients with this disease sometimes developed hemarthroses, but in two adult patients the same degree of degenerative arthritis as is usually seen in hemophiliacs of the same age group was not observed. 1711

RHEUMATIC (HENOCH-SCHÖNLEIN) PURPURA

In an attempt to give this strange and intriguing syndrome a more descriptive name, the terms "anaphylactoid purpura," 1256, 2180 "nonthrombocytopenic purpura" 1406 and "acute vascular purpura" were proposed. 1164 The development of the syndrome since its first description in 1808 was traced by Jensen, 1042 who noted that Osler in 1904 first dealt with its resemblance to allergic disorders; it was now generally classified in this group of diseases. This, plus the fact that the chief pathologic lesion was apparently an angiitis with a perivascular exudate, 1164 indicated a more than coincidental relationship to disseminated lupus erythematosus and periarteritis nodosa. 1042, 1164, 1256

The characteristic skin lesions of urticaria progressing to coalescent purpuric areas on the exterior surfaces of the extremities, the flexion folds of the elbows and the gluteal and perigenital regions were of interest because of the normal blood

findings (including "bleeding" factors). The abdominal symptoms may simulate a "surgical abdomen," and differentiation is important, since surgery was indicated only when perforation or intussusception was suspected. 1042, 1496 Joint symptoms varied from slight pain in a single joint to intense pain and periarticular swelling of several joints. Renal symptoms of hematuria, albuminuria and cylindruria resembling acute glomerulonephritis frequently occurred and might precipitate a fatal outcome.2180 The condition was found in young children as well as adults; those under six years of age were less likely to develop serious renal lesions than those over six.2180 The precipitating allergen might be a particular food, or a drug, but was most frequently an upper respiratory infection. An attempt was made to determine the offending agent in an effort to avoid future attacks. The acute phase of the disease was controlled by ACTH; if relapse followed its discontinuance, resumption of therapy for a longer period of time was recommended. 281, 2157 Renal sequelae, however, sometimes were resistant.2180 A case of Henoch-Schönlein syndrome coexisting with familial hereditary purpura simplex was reported. 2157 Another interesting report 452 documented a case of Henoch-Schönlein syndrome due to quinine that developed erythrophagocytosis and a serum factor which could induce erythrophagocytosis in normal blood, as well as other immunohematologic phenomena.

ALKAPTONURIA, OCHRONOSIS AND OCHRONOTIC ARTHRITIS

The rarity of this condition was illustrated by the fact that the diagnosis was made only 12 times at the Mayo Clinic between 1927 and 1953. Five other papers reported a total of 11 cases. 188, 688, 1264, 1940, 2279 All reviewed existing knowledge of the disease and noted the predilection for spinal arthritis with degeneration and calcification of intervertebral discs. A report of the removal of a ruptured ochronotic intervertebral disc was included. Pathologic changes in two necropsies were recorded. [A discussion of the nature of the metabolic defect and genetic aspects of this abnormality was recently published. 1191—Ed.]

PALINDROMIC RHEUMATISM

Analysis of the synovial fluid in a case of palindromic rheumatism showed no distinct electrophoretic pattern; the protein distribution was similar to that of various acute arthritides.²²⁴¹ A case of palindromic rheumatism, apparently psychosomatic in origin, was discussed, and the "psychodynamic formulation of the patient's illness" was presented in some detail.³¹ [See Rheumatoid Arthritis section.—Ed.]

TEMPOROMANDIBULAR JOINT PAIN (INCLUDING COSTEN'S SYNDROME)

"The diagnosis and treatment of temporomandibular joint pain and dysfunction is a challenging undertaking requiring knowledge, patience and skill." ¹⁸⁴² "Diagnosis is rarely clear-cut or definitive." ¹⁵¹⁵ So-called "Costen's syndrome" included not only pain in the joint itself but also clicking noises, facial pain and middle ear symptoms of tinnitus, vertigo and impaired hearing, presumably due to posterior displacement of the condyle. ⁵⁹¹ Causes of painful syndromes affecting the temporomandibular joint were usually listed as congenital, inflammatory, traumatic or neoplastic. ¹⁸¹⁵

A survey of 500 cases in five years at the Temporomandibular Joint Clinic (a research clinic of the Division of Clinical Oral Physiology of the Dental School,

Columbia University), in coöperation with various departments of the Presbyterian Medical Center, showed a low incidence of organic diseases and pointed to a functional disorder. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment. Local anesthetics followed by therapeutic exercises were often effective in treatment.

PHARMACEUTIC ARTHRITIS AND ARTHRALGIA

Hydralazine Syndrome. One of the most fascinating developments in the field of rheumatic diseases which has occurred in the past several years has been the development of rheumatoid symptoms in patients receiving hydralazine hydrochloride (Apresoline) as a therapeutic agent for hypertension. Several papers reported this in some detail, 570, 646, 1346, 1498, 1615, 1835 and the pertinent data were summarized in the Bulletin on Rheumatic Diseases. 1216 Approximately 10% of patients receiving 600 mg. or more of hydralazine daily for one year or longer will probably develop the syndrome. Initially, chills and malaise with migratory joint and muscle pains were observed, soon followed by inflammatory joint changes, often with symmetric involvement of the proximal interphalangeal finger joints practically indistinguishable from rheumatoid arthritis. If administration of hydralazine was continued, a febrile phase developed which might be manifested by fever, prostration, serous cavity effusions, lymphadenopathy, splenomegaly and erythematous rashes. In this stage, the syndrome resembled acute disseminated lupus erythematosus. Indeed, L.E. cells were found in blood smears. The exact mechanism by which the syndrome is produced remained obscure. Since only 10% of the hydralazine-treated cases were so affected, some additional factor seemed involved, but an allergic or sensitization mechanism seemed unlikely. Since the hypotensive action of hydralazine is believed to be mediated by its action on the midbrain, the syndrome may be the end result of a pharmacologically altered midbrain function. [Intriguing fields for investigation which are presented by the syndrome are immediately apparent, for it is the nearest approach to the experimental production of a rheumatic state in presumably otherwise nonrheumatic individuals so far discovered.-Ed.]

Allergic Arthritis. Various foods and drugs (notably penicillin) may cause temporary joint swellings as part of an allergic reaction. Treatment included removal of the precipitating allergen, use of epinephrine, antihistaminics and ACTH. 88, 1489, 1895, 1980 An allergic granulomatous arteritis, similar to periarteritis nodosa, was precipitated by penicillin. 605 [See Polyarteritis Nodosa section.—Ed.]

OTHER TYPES OF ARTHRITIS AND ARTHRITIC SYNDROMES

Intermittent Hydrarthrosis. This condition may be more common than is suspected, and be mistaken for true rheumatoid arthritis, 2266 or it may be the early stage of a true rheumatoid arthritis, 515 or the two may coexist. 508 [It is most likely a phase of rheumatoid arthritis.—Ed.] Sex hormones were said to be of value in treatment. 5268 When affecting the hips in children it was commonly referred to as "transient synovitis." [But without adequate evidence.—Ed.] Transient synovitis of the hip was a self-limiting disease and usually cleared within several days. 588, 952

Sjögren's Disease (Gougerot-Sjögren; Sicca Syndrome). Dryness of the eyes and mucous membranes, with enlargement of the parotid gland associated with dental caries and rheumatoid arthritis, formed the classic picture of Sjögren's disease. How-

ever, achylia gastrica, hypochromic anemia, Raynaud's phenomena and scleroderma also occurred with the "sicca syndrome." Biopsy of a parotid gland of a 49 year old woman showed "previously undescribed units of cells in reticular arrangement between the lining epithelium and basement membrane of the ducts." It was suggested that these could be causally related to the atrophy of the secreting portion. This paper reviewed the syndrome in some detail and mentioned its importance to the internist. The condition may not be so rare as was formerly thought, for evidence was found in 40 of 456 cases of rheumatoid arthritis at the Anti-Rheumatic Center in Amsterdam. The authors of both of the papers quoted used cortisone as a therapeutic agent, with rather incomplete success.

Arthritis Mutilans. This uncommon destructive joint disorder affected the hands and fingers, the feet and toes. The involved digit resembled the sections of an operaglass, and has been designated "doigt" (finger), "main" (hand), or "pied (foot) en lorgnette." A case unaccompanied by psoriasis occurring in a 17 year old male was reported. Changes were limited to the feet. Biopsies from an affected digit showed extensive fibrosis, vascular sclerosis and osteolysis. It was concluded that this condition was not an advanced stage of rheumatoid arthritis and should be considered as a separate entity. [We do not agree with this opinion.—Ed.]

Tietze's Syndrome. In 1921 Tietze reported four cases of a syndrome characterized by "swelling of the costal cartilages, of unknown etiology, insidious in onset, spontaneously painful, not associated with constitutional disturbances and of a prolonged fluctuating course." In four cases resected surgically the cartilage was not diseased, but buckled forward by the contracted ligament which lay subjacent to the second costal cartilage, the one most frequently involved.¹³² Four cases were reported.²¹⁸⁴ [Steroids have recently been used to advantage in these patients.—Ed.]

Behçet's Syndrome. Behçet's syndrome consists of recurrent genital and oral ulceration, with eye lesions and at times skin lesions resembling erythema nodosum and joint symptoms resembling rheumatoid arthritis. Twelve cases were reported, 1626 and in four cortisone and corticotrophin were apparently helpful therapeutic agents. The joint lesions were nonarticular, with the same joint affected during exacerbations; knees, ankles and wrists were most commonly involved. It was suggested that the condition might "eventually fall into place among the collagen diseases."

Erythema Multiforme. Stevens-Johnson Syndrome. A case of erythema multiforme exudativum major and a review of the literature were presented.²⁵ The pathogenesis of the condition was apparently an abnormal antigen-antibody reaction. ACTH was the most effective treatment.

Erythema Nodosum. Two cases were reported, one successfully treated with cortisone. 995, 2268

THE PAINFUL SHOULDER

As was pointed out in the Eleventh Rheumatism Review, some order is gradually emerging from the confusion which has so long surrounded those conditions in which the common denominator is pain localized in the vicinity of the shoulder joint. The great variety of terms formerly used has to a large extent given way to a few generally accepted names, and there is increasing agreement on many points, therapy being probably the most notable exception.

The use of the term "painful shoulder" as an over-all designation was preferred by most writers, although various other terms were also used. The word "omodynia" (Gr. omo = upper arm and shoulder + Gr. dynia = pain) was introduced by Crain. 450 An excellent summary of the problem was presented by Steinbrocker. 2001

Although many writers made no attempt to separate various entities but discussed different "phases" of the painful shoulder syndrome, most writers agreed on at least four distinct entities. These, as well as others in which there was less universal agreement, will be discussed separately. [Referred shoulder-tip pain from irritation of the central part of the diaphragm or irritation of the phrenic nerve has not been included in this review.—Ed.]

Calcific Tendinitis. This condition evoked more universal agreement than did any other in this group. The old appellation, "bursitis," has gradually given way to the more descriptive term, "calcific tendinitis." However, since bursal and tendon lesions frequently coexist, differentiation was considered to be more academic than practical. 1937

The acute stage, with sudden onset, agonizing pain, sharply localized tenderness and limited motion, made diagnosis fairly easy. The subacute and chronic stages, which may or may not be preceded by one or more acute episodes, are more often represented by aching pain and low grade, persistent disability; tenderness and limitation of motion are less marked. In either, the x-ray showed deposits of calcium ranging in size from single, barely discernible "flecks" to multiple chunks approaching the size of golf balls. The cause of the calcific deposit as well as that of the acute, painful episode remained enigmatic. Most writers who hazarded an opinion suggested the chief etiologic factor to be degeneration of the supraspinatus tendon due to a "fraying action" as it passes under the tip of the acromion. 438, 407, 848, 1086, 1413, 1037 Olsson's studies, however, suggested that painful lesions were not necessarily related to degeneration, but were more dependent upon immobilization. 1560, 1561 [Degenerative lesions failed to explain the not uncommon occurrence of the condition in younger persons.—Ed.]

Previously described treatments again recommended included x-ray therapy, 757, 1890 acetic acid ionization, 1667 needling, with or without procaine injections, 820, 848, 1221, 1415, 1937 and a variety of other therapeutic procedures. 1937 Hydrocortisone injections were usually rather highly recommended. 808, 439, 454, 1571, 1724, 1802 Oral phenylbutazone was found to be quite helpful in relieving pain. 486 In addition, a modality new during the period covered by this Review (at least to American physicians) was discussed, namely, ultrasonic "sounding." As might be expected, opinion as to its effectiveness was far from uniform, and ranged from "the treatment of choice" 23, 24, 726 to "of no value," 1493 with most writers favorably but cautiously impressed. 847, 1238, 1234, 1839, 1840 The exact means by which ultrasonic radiation produces its beneficial effect is unknown. A thermal effect is most apparent and may be the principal factor. However, other effects—biologic, chemical and mechanical—may be as important. 569, 726, 1889 Earlier misgivings about the dangers of ultrasonic therapy seem unwarranted, and its use is apparently no more hazardous than is that of diathermy. [Although a comprehensive review of this therapeutic modality is beyond the scope of this Review, physicians will do well to acquaint themselves with certain fundamental concepts, since the attention given ultrasonics in the lay press has made patients acutely conscious of its purported therapeutic values. It is more dangerous than diathermy, particularly when used over nerves or the spinal cord. Whatever the final evaluation of this modality may be, it seems destined to have an adequate trial, for reports indicate widespread usage. See also section on Rheumatoid Arthritis, Treatment.-Ed.]

Bicipital Tenosynovitis. Although all writers were not in agreement, most recognized acute symptoms of pain and tenderness over the bicipital groove as due to a localized inflammatory lesion of the long head of the biceps. The cause of such inflammation is not entirely understood, but is probably due to attrition from continued gliding of the tendon in the intertubercular groove and

adjacent structures. 497, 504, 505 Two cases were recorded where a coracobrachialis brevis, one of the common anatomic variations of the coracobrachialis muscle, apparently influenced the onset of symptoms. When present, this muscle inserts on the upper portion of the shaft of the humerus and presents a mechanical obstruction to the motion of the lesser tuberosity on internal and external rotation of the humerus. On physical examination, pain was demonstrated on performance of these motions, with definite, persistent tenderness over the lesser tuberosity. 129

Treatment consisted of localized procaine injections and active physical therapy, the principal object being to keep the shoulder joint mobile and so prevent the development of a frozen shoulder. Oral cortisone was reported to expedite relief of pain. Operative excision of the coracobrachialis brevis.

when present, was effective. 120

Adhesive Capsulitis. This was the third painful shoulder entity on which there was rather general agreement. [Although most writers continue to use the term "frozen shoulder," this would seem a rather unsatisfactory designation, since only a small percentage of the cases progress to complete immobilization.—Ed.] In contrast to calcific tendinitis, adhesive capsulitis usually develops rather slowly, with generalized, dull aching pain, diffuse minor tenderness, and gradually increasing restriction of glenohumeral motion. In some cases the joint becomes completely "frozen." This may occur as a sequel to any painful shoulder condition which causes restriction of motion, but is most likely to follow bicipital tenosynovitis. ^{504, 505, 2116, 2265} In a series of 72 cases, only one was under 40 years of age. ⁵⁰⁵ An important factor in development of the condition was said to be a "periarthritic personality," since shoulder pain seemed to develop particularly in persons with passive, apathetic attitudes and poor tolerance of pain.

Recommendations for treatment centered about physical therapeutic modalities designed to increase motion of the joint. 648, 1154, 1221, 1714, 1800, 2116 In the early stages, procaine infiltrations of tender areas were helpful, 1920, 1921, 2265 as were ethyl chloride spray to the shoulder area 1800 and intra-articular hydrocortisone. 808, 455, 1724 In a comparative trial of the effects of local injection of hydrocortisone in 24 patients and lidocaine hydrochloride (Xylocaine) in 27 patients, neither substance showed any advantage over the other. 1502 Forceful manipulation under anesthesia was mentioned by some "only to be condemned"; 505, 717, 785, 2265 nevertheless, it still had surprisingly many supporters. 1449, 1678, 1714, 1802, 2015 ACTH and cortisone were suggested as useful adjuncts to manipulation. Surgical intervention, by severing the long head of the biceps brachii tendon and then anchoring it to the coracoid process or the shaft of the humerus, was resorted to in long-standing chronic cases. 508, 2116 One author felt that no treatment could affect the course of the disease, and claimed that all cases recover in 12 to 18 months, with or without treatment. 785

Musculotendinous Tears. Tears of the musculotendinous cuff of the gleno-humeral capsule accounted for a large percentage of cases of shoulder pain. 270, 1086 These cases usually presented with sharply localized pain and tenderness coming on after exercise, often in middle aged patients. It was observed that if the tear was of moderate size, carefully graded exercises sufficed to keep the shoulder mobile until healing occurred; large tears and massive avulsions required surgical repair. Roentgenographically demonstrable cystic degeneration of the humeral

tuberosity was a common accompaniment of tears. 1860, 1861

Miscellaneous Shoulder Conditions. A further cause of pain in the region of the shoulder was fibrositis affecting the trapezius and deltoid muscles. Acromioclavicular joint pain was occasionally noted, and was usually relieved by procaine infiltration. 936 Postural syndromes, called by various names, including "scapulo-costal syndrome." 446, 1049, 1442, 1800 were considered to be frequent causes of shoulder pain in middle-aged persons. Russek 1800 described this syndrome as a clinical entity in which symptoms manifested themselves in one of several regions: (1) root of the neck, with radiation outward across the shoulder and down the arm to the fourth and fifth fingers; (2) girdle-like pain, beginning in the scapula and radiating around the chest to the sternum; (3) radiation of pain up the neck to the occiput; (4) pain at the shoulder alone, without radiation. Trigger points along the vertebral margin of the scapula and muscle spasm of the trapezius when the symptoms were chronic completed his description of this condition. [No clear distinction can yet be made between this scapulocostal syndrome and "fibrositis," "fibromyositis" or "fasciitis" as causes for pain in the shoulder area. As psychogenic rheumatism becomes a more recognized diagnosis there is less tendency to use terms which imply structural changes in patients with pain in the shoulder girdle.-Ed.] Treatment consisted of physical therapy, postural exercises and procaine infiltration into tender areas. Normal saline might be as effective as procaine. 1980

Rheumatoid Arthritis may be a more common cause of painful shoulder than was previously thought, having been found to affect the shoulder in 47% of a series of 277 unselected hospitalized patients with proved generalized rheumatoid arthritis. 1200 Pulmonary tuberculosis must also be considered in the differential diagnosis. In a group of 260 patients hospitalized for pulmonary tuberculosis, 24.2% of those over 40 years of age (but only 1.6% of those under 40) developed pain and limitation of motion of the shoulder. Immobilization incident to bed-rest was apparently an important factor in the development of symptoms. 11 In two reported cases of a form of "baseball shoulder," an injured and indurated area in the fascia beneath the deltoid muscle was removed. After its removal, the men were able to resume the playing which had been interrupted by the spontaneous development of pain in the shoulder. 1464

SHOULDER-HAND SYNDROME (REFLEX SYMPATHETIC DYSTROPHY)

Steinbrocker, the originator of this term, again summarized existing knowledge of this clinical syndrome. 2001, 2008 An initial stage of hyperemia, characterized by brawny and diffuse swelling of the fingers, hand and wrist, accompanied by painful limitation of shoulder motion, may persist for months. Gradual healing, either partial or complete, may take place, or the condition may progress to result in trophic changes including flexion deformities of the fingers due to loss of elasticity in the periarticular tissues, muscular atrophy, Dupuytren's contracture and a frozen shoulder. 1909 But a characteristic pattern was found to be far from uniform. Either or both sides may be affected, and atypical cases may present involvement of the hand but not of the shoulder, or vice versa, or even atypical localizations of pain. 1648 The syndrome was most commonly observed following myocardial infarction, 151, 1285, 1648, 1828, 1909 but it also followed any condition in which the arm was immobilized for prolonged periods. posthemiplegic shoulder-hand syndrome presented special problems. 1170, 2048 A case following herpes zoster was reported. 1782 The symptoms may start from a few weeks to many months after the precipitating factor; psychologic factors evidently play an important role in its initiation, 924, 2008

The pathology remains obscure. The theory of de Noe (discussed in previous Rheumatism Reviews) was reiterated, that painful stimuli bombarding the "internuncial pool" of neurons eventually set off a "self exciting chain" of impulses in the spinal cord giving rise to the neurovascular changes seen in the tissues of the affected extremity.448, 1660, 2008 A refreshingly new, simple and logical explanation was advanced by Moberg, 1465 who felt that the primary pathologic factor was immobilization, with resultant absence of the "pumping mechanism" of the return blood flow, and consequent stasis. One author 525 suggested painful lesions of the soft tissues in the lower back as a cause. Treatment was admittedly far from satisfactory. Stellate ganglion block was still recommended, 1818 but apparently with less enthusiasm than formerly. 2003, 2211 Carefully controlled physical therapy remained essential to proper management. 1660, 2008, 2196, 2211 Steroid therapy was a valuable adjunct. 1538, 2008 One author claimed 100% relief in 18 cases by injecting hydrocortisone into painful trigger points. 151 [This needs to be confirmed.—Ed.] Early, passive mobilization of a hemiplegic extremity was recommended as an aid to prevention of the syndrome, 1170, 1285

BRACHIAL NEURALGIA

The variety of rheumatic conditions which will produce a radicular type of pain or paresthesias in one or both upper extremities drew the interest of those in neurology and neurosurgery, orthopedic surgery, internal medicine and general practice as well as rheumatology. "During the last half century scores of papers have been written on pain in the upper extremity but it is evident that the problem today lacks satisfactory resolution." 1677 "The accurate diagnosis and effective treatment of disabilities manifested by cervico-brachial pain and paresthesia is difficult." 1049

Although a rational analysis of the anatomy of the nerves and blood vessels of the upper extremity will indicate logical points at which irritation of these structures might be expected to occur, localization in a particular case may be extremely difficult. "To the confusion of examiners, specificity of names in cervico-brachial syndromes is not matched by a specificity of either signs or symptoms." 1040

Several excellent reviews of the subject were presented.^{158, 252, 448, 998, 1862} One of these ⁹⁹⁸ presented an interesting study of 277 industrial and forest workers surveyed in great detail for skeletal complaints. Analysis of the material presented in the papers indicated that interest centered primarily about three regions: the cervical spine, the scalene tunnel, and the superior thoracic outlet.

Disc degeneration of the cervical spine, with or without disc protrusion, was the most obvious cause of brachial neuralgia. Nevertheless, several confusing and contradictory factors arise. First, there was the question of how much importance could be attached to the x-ray appearance. Although osteophytic formations narrow the intervertebral neural foramina, rather extensive changes were frequently unaccompanied by symptoms. Second, narrowing of the intervertebral space apparently did not always indicate disc protrusion. 586, 998, 2082 For best visualization, lateral x-rays in flexion and extension were advised. Too A third—and interesting—question which has recently again been raised concerns the existence or nonexistence of the joints of Luschka and their relationship to this condition. According to the descrip-

tion of Luschka in 1858, true joints exist at the posterolateral border of cervical vertebrae two to seven, the articulation being formed by "the neurocentral apophysis below and the inferolateral aspect of the vertebral body above." Although most authors ignored these joints completely, apparently doubting or being unaware of their existence, others considered them to be of extreme importance as the chief site of osteoarthritic changes in the cervical vertebrae. The standard standard the sanatomic debate is interesting, it is not of particular significance from a practical therapeutic standpoint since, joint or no joint, osteophytes in this region tend to encroach upon and to narrow the intervertebral neuroforamina and so to form a basis for the pro-

duction of symptoms.

The actual status of the intervertebral fibrocartilage was of somewhat greater importance. Two types of lesions may be recognized. The first, a true herniation of the nucleus pulposus, usually traumatic in origin, was the so-called "soft disc lesion"; the other was a posterior (or anterior) bulging or protrusion of the annulus fibrosus, due to a degenerative change and producing the "hard disc lesion." The existence of a disc lesion may be difficult to determine without myelography.^{278, 448} Posterior protrusion may cause symptoms in the lower extremities, including the presence of Babinski's sign and a reduced sense of position. The entire problem assumes importance from the medicolegal angle because of the frequency of "whiplash" injuries. Although such injuries rarely produced fractures of bone (or, indeed, ruptured discs),¹²⁷⁷ they formed the basis for persistent complaints of pain in the neck and shoulder with occipital headache. However, not all such cases show organic lesions. An analysis of 800 cases from one physical therapy clinic listed 317 cases as due to "tension neck." In these patients, "typical cervical symptoms were associated with environmental factors producing tension." ^{1160, 1171}

Treatment recommended was somewhat uniform. Conservative measures included physical therapy (with or without cervical traction) and the occasional use of a cervical collar. Postural exercises were stressed.^{448,700} Procaine block of the suprascapular nerve at the suprascapular foramen helped some cases.¹⁹²¹ X-ray therapy over the spine produced relief,¹⁶⁸⁸ as did ultrasonic treatment.¹¹⁸⁰ Because these conditions seemed to develop in patients "with a personality that is refractory to treatment and whose tolerance to pain is low," the physician was advised to insist on a rigid schedule and assiduously avoid the use of narcotics.⁴⁴⁸

Automation seems to have come to the field of physical therapy in the form of a machine which applies cervical traction intermittently. 1076, 1510 It was agreed that if conservative treatment failed, myelographic studies were indicated, with operative intervention when definite nerve impingement is determined.

High cervical chordotomy was performed for intractable pain.988

As the nerves pass lateralward from the spinal column to form the cervical plexus and then differentiate into specific nerves to supply the arm, shoulder and chest wall, they come into intimate relationship with the blood vessels supplying these same areas. The space which nature normally allots to these particular structures is never great; hence, any encroachment on that space may produce symptoms. Such obstructions were again noted as being due to a cervical rib, anomalous fibrous bands or anomalous muscle insertions, 1677 hypertrophied scalene muscles or developmental and postural narrowing of the space between the clavicle and first rib. 712, 1049, 1863 Differentiation by symptoms alone was difficult. These ranged from simple aching in the arm, with occasional numbness and tingling, to complete disability from constant severe pain, with

vascular impairment and trophic changes. The various maneuvers designed to cause temporary obliteration of the radial pulse (described in some detail in the last Rheumatism Review) continued to be helpful but not infallible, since they were sometimes positive in persons without symptoms, and vice versa. 448, 2258

In connection with pain experienced in the neck, shoulder and arm, studies of referred pain are of interest. Such studies indicated that the shoulder apparently derives its nerve supply from C-5 to C-8. 1580 Experimental injection of paravertebral muscles of the neck and back with hypertonic saline solution demonstrated that the muscles in which the referred pain was apparently felt derive their approximate motor-nerve supply and possibly their sensory-nerve supply from the segment stimulated. 604

Conservative treatment recommended for this group of conditions included physical therapy, postural exercises and cervical collar, as outlined above for arthritic and disc lesions. If these fail, surgical exploration is in order. Anterior scaleniotomy or removal of a cervical rib may be sufficient, but because of the possible concurrent existence of other conditions should not be performed without exploration of the entire area. 448, 1297, 1077, 1862, 2253

NONARTICULAR RHEUMATISM

This term was used to refer to a large group of disorders with musculo-skeletal aches and pains about joints and in nonarticular soft tissues, but without disease of the joint structures proper. "Fibrositis" and "nonarticular rheumatism" are not used as synonymous terms in this Review. The various forms of nonarticular rheumatism constituted the largest single group of rheumatic diseases, 826, 827, 1111 and accounted for the attendance of about one in every four patients at arthritis clinics in the United States. 2192

Bursitis. Usually a primary disorder, bursitis was occasionally secondary to rheumatoid arthritis, gout, the "collagen diseases" and others. ¹²¹ Primary bursitis was most often nonspecific, but tuberculous ¹⁶⁸¹ and brucellar ¹⁰⁵⁰ and coccidioidal bursitis ²¹⁵⁰ were reported. Primary nonspecific bursitis usually occurred about the shoulder, but was found also in the olecranon, the ischial and Achilles bursae, and in those about the hip, knee, wrist, fingers and toes. ¹²¹ loss Radiohumeral bursitis was implicated as one of the causes of "tennis elbow." ¹⁵⁰¹, ¹⁶⁷⁴, ¹⁶⁷⁵ Calcific bursitis, most common about the shoulder, resulted from rupture into the subacromial bursa of calcific deposits from areas of degeneration in the rotator cuff tendons. ¹²¹, ¹⁰²⁸, ¹⁴¹⁸, ¹⁸⁹⁰ [See Calcific Tendinitis in the section on the Painful Shoulder.—Ed.] Calcific bursitis was also reported about the hip ⁸⁸⁹, ¹⁰⁸¹ and in the pisiform bursa. ²²⁸⁶

Basic treatment included analgesics, hot or cold applications, rest and immobilization in the acute stages, and exercises as pain subsided. Hydrocortisone injections gave prompt, striking relief in acute cases but less consistent results in chronic ones. 77, 121, 454, 1028, 1187, 1724, 1802, 2272 Deep roentgen 889, 1184, 1683. 1890 and ultrasonic therapy 23, 24, 847, 1000 were also considered to be valuable, though in one study controls fared as well as those treated with ultrasound. Benefit was reported from mephenesin and glutamic acid hydrochloride, 780 and intracutaneous histamine. 1612 [These require confirmation.—Ed.] Excision of calcific deposits, 121, 1028, 1418 and manipulation under anesthesia for chronic bursitis

with "frozen shoulder," 77, 121 were advocated if disability persisted after other treatment. Tuberculous and brucellar bursitis were treated by surgical excision and streptomycin, para-aminosalicylic acid (P.A.S.) and isonicotinic acid hydrazide (I.N.H.) for the former, and Aureomycin and dihydrostreptomycin for the latter. 1050, 1631

Tenosynovitis and Tendinitis. Clinical, pathologic and electron microscopic features of rheumatoid tendon lesions were described.¹¹¹¹ Tenosynovitis occasionally was found to mark the onset of systemic rheumatic disease.⁹⁰¹ With improved treatment and prevention, suppurative tenosynovitis had almost disappeared as a cause of disability.⁶⁰ Proved tenosynovial coccidioidomycosis in one patient clinically and pathologically resembled tuberculous tenosynovitis.²¹⁵⁰

Nonspecific tenosynovitis in the flexor compartment at the wrist occasionally caused median nerve compression producing the so-called "carpal tunnel syndrome." This syndrome of median neuropathy at the wrist also occurred spontaneously and as a result of other lesions in the carpal region.^{687, 980, 1210, 1803, 1883, 1830, 2103, 2236}

Stenosing Tenosynovitis. Adults with stenosing tenosynovitis showed the major pathologic changes in the tendon sheath; in children, however, collagenous degeneration of the enclosed tendon was marked, and changes in the sheath were only minimal.^{652, 2212}

De Quervain's Disease. A useful diagnostic test was Finkelstein's sign: the severe pain produced by flexing the thumb into the palm, closing the fingers over it, and deviating the wrist toward the ulna. 869, 446, 960, 1581 Anomalous arrangements of the abductor pollicis longus and extensor pollicis brevis tendons and their sheaths predisposed to de Quervain's disease. 47, 2108, 2212 In one case, such anomalies were considered to be the cause of snapping and locking, a phenomenon rarely observed in de Quervain's disease. 278

Stenosing tenosynovitis also affected the sheaths of the thumb and finger flexor tendons, and the extensor sheaths on the dorsum of the wrist. Locking of the digit, "trigger finger" (or thumb) in flexion, and snapping and clicking on movement were common manifestations. In infants, the flexor pollicis longus sheath was almost exclusively involved.^{47,446,682,2103}

Stenosing tenosynovitis rarely involved the sheaths of the tibialis anticus and posticus, peronei and flexor hallucis longus at the ankle.^{369, 531}

Calcareous Tendinitis. Most common in the rotator cuff tendons of the shoulder, where calcium was deposited in areas of tendon degeneration, calcareous tendinitis resulted in inflammation and pain, varying from intense and acute to low grade and chronic, but frequently terminated in spontaneous recovery. Only 30% to 45% of persons with soft tissue calcifications about the shoulder gave a history of any shoulder discomfort. A similar process also occurred in tendons, joint capsules, ligaments and other connective tissues about the hip, elbow, knee, wrist, hand, fingers and toes, and in the ligamentum nuchae. 121, 229, 845, 497, 1061, 1341, 1418, 1884 Pisiform-triquetrous sprain presented a clinical picture similar to that of calcareous tendinitis of the flexor carpi ulnaris insertion. 1983 Possibly related to calcareous tendinitis was Pellegrini-Stieda disease, in which the calcification was probably located in different tissue sites adjacent to the adductor tubercle of the femur on the medial side of the knee. 487, 1511 Two cases with deposition of calcium salts in the popliteal tendon on the outer side of the knee were described. 976

Noncalcific Tendinitis of the common tendon of origin of the forearm extensors at the lateral humeral epicondyle was considered to be responsible for some cases of "tennis elbow."

Treatment. Basic treatment of tendinitis and tenosynovitis consisted of rest, immobilization of the part, analgesics, heat, diathermy, and graded exercises as pain

subsided. Local hydrocortisone injection was widely recommended. 77, 121, 289, 448, 454, 497, 1187, 1501, 1674, 1675, 1724, 1802, 1972, 2272 Ultrasonic therapy 23, 24, 446, 847, 1080 and roentgen therapy, particularly for acute calcific tendinitis, 121, 229, 487, 1134, 1841, 1511, 1833, 1890 also gave benefit in some cases. Less generally accepted treatments included intramuscular adenosine-5-monophosphate (for calcific tendinitis), 2042 and intracutaneous histamine. 1612 Stenosing tenosynovitis often necessitated excision of the affected sheath and early postoperative mobilization. 47, 852, 960, 1028, 1581, 2108, 2212 Surgical removal of calcific deposits was recommended for "hyperacute" calcareous tendinitis and for cases failing to respond to conservative treatment. 121, 487, 497, 1341, 1413, 1511 In one study, "tennis elbow" responded no better to local hydrocortisone injection than to local procaine. 716 Resection of the orbicular ligament of the radius and division of the common extensor origin completely relieved five patients with "tennis elbow" after failure of other measures,286 The treatment of choice for tuberculous tenosynovitis was surgical excision of all involved tissue, with secondary tendon reconstruction at a later date.960 One case of tuberculous tenosynovitis was apparently cured by isoniazid after failing to respond to streptomycin and para-aminosalicylic acid therapy.809

Fasciitis and Fascial Fibromatosis. It was increasingly emphasized that Dupuytren's contracture was the palmar manifestation of a fascial fibromatosis which might also involve other areas in such forms as dorsal knuckle pads, fibromatosis of the plantar fascia and Peyronie's disease. 27, 29, 244, 426, 904, 1554, 1601, 1768, Bilateral palmar and plantar fibromatosis was reported in a 14 year old boy. 707 In 80 patients with Dupuytren's contracture, the finding of an identical Rh blood type suggested an inherited predisposition to the disease among persons with this blood grouping.829 [This interesting observation merits further investigation.-Ed.1 Enlarged Pacinian corpuscles observed in diseased areas of fascia prompted the theory that the contracture may be due to asynergy of the vascular and autonomic nervous systems.262 [A highly theoretic proposal, requiring confirmation.-Ed.] The association with epilepsy described in previous reviews was now infrequent or absent.29, 426, 815, 2269 In three tuberculous patients, isoniazid was implicated as the cause of a "Dupuytren's-like contracture," peripheral neuropathy and neurovascular dystrophy of the hands. 968 Surgical excision of affected fascia was the treatment of choice. 27, 29, 244, 426, 904, 1212, 1554, 1601, 1781, 2114 Cortisone was said to permit earlier mobilization and to improve surgical results,154 though its value in these respects remained to be definitely established. Local injection of hydrocortisone, 454, 797, 2282 and x-ray therapy or radium mould application, 426 were tried in the early proliferative stages of the disease and in cases unsuited for operation. Vitamin E was of no value.27, 244, 426, 1212, 1554 Painful heels due to fasciitis or strain of the plantar fascia at its calcaneal attachment were treated by adhesive strapping and insoles to relieve the fascial strain. 1778, 2254 Hydrocortisone injection in such cases had no lasting benefit. 464, 1802 Possibly related to fascial fibromatosis was an unusually dense collagenous fibrosis of the flexor digitorum sublimus in the forearm producing a flexion contracture of the fourth finger. 1446 [Dupuytren's contractures with fasciitis are common manifestations of rheumatoid arthritis.-Ed.]

Synovial Cysts. A large, horseshoe-shaped Baker's cyst due to enlargement and fusion of medial and lateral popliteal bursae was described. Persistent disability after removal of Baker's (popliteal) cysts resulted from unrecognized meniscus tears which in three patients were the primary cause of the cyst formation. Personnel Cysts formation.

Ganglia were said to arise from joint or tendon sheath synovium and were due to extrusion of synovial secretion, with compression of surrounding tissue and formation of a fibrous pseudocapsule. At times, ganglia at the wrist caused ulnar nerve compression, with accompanying loss of sensory and/or motor function of ulnar distribution in the hand. Aspiration and injection with hydrocortisone, 446, 1730, 1972 a sclerosing solution 1402 or surgical excision if disability persisted was recommended.

Calcinosis. The relationship of calcinosis to "mesenchymal diseases" such as rheumatoid arthritis, dermatomyositis and scleroderma was again stressed.

55, 423, 1416, 1848, 2155 Additional cases of circumscript ⁸⁷² and universal calcinosis

55, 1416 were described, in one of which cortisone had no apparent benefit. ¹⁸⁴⁸ An unusual heredofamilial vascular and articular calcification was reported in two of the four offspring of consanguineous parents. ¹⁸⁸⁰ Periarticular calcifications in two patients with encephalomyelitis, and in one after craniotomy for a brain tumor, were considered to result from a process similar to localized myositis ossificans. ²⁰⁸¹

MYOSITIS AND MYALGIA

Myositis Ossificans. Experimental studies indicated that localized myositis ossificans resulted from connective tissue metaplasia rather than from migration of osteoblasts from traumatized bone or periosteum. Localized heterotopic ossification occurred in upper abdominal operative scars in six patients, late and in association with rheumatoid arthritis, tabes dorsalis, myelitis, syphilitic meningomyelitis, syringomyelia, paraplegia, hemiplegia and poliomyelitis. Late and poliomyelitis. Late and poliomyelitis of times resembled osteogenic sarcoma or fibrosarcoma. Stiffness and immobility were attributed to degeneration, inflammation and fibrosis of soft tissue rather than to actual bone formation. Late Additional case histories of myositis ossificans progressiva were reported. Additional case histories of myositis ossificans progressiva were reported. Cortisone or ACTH was advocated for relief during exacerbations, but one patient's disease was uninfluenced by these hormones.

Epidemic Myositis or Myalgia. (Epidemic Pleurodynia: Bornholm Disease). The causative role of *Coxsackie* viruses of group B (Dalldorf) types one and three, and possibly two and four as well, was confirmed. Sharply localized epidemics in summer or early autumn occurred in both urban and rural distribution. Endemic areas were also reported. Density of infection was not usually affected by socio-economic conditions, race or sex. The virus was isolated from the feces and sometimes from the throats of patients, from sewage and flies. Spread was by direct contact, the usual incubation period being from three to five days, with a range of from one to 18 days. 185

Polymyositis was generally considered to be the same basic disorder as was dermatomyositis without cutaneous changes. 596, 1919 Pathologic and electromyographic features were said to be diagnostic, 581, 1204 but their specificity was questioned. Closely related to if not identical with polymyositis was the so-called "menopausal muscular dystrophy." 225, 581

Myalgia and Myalgic Spots. Stimulation of so-called "trigger-points" was said to cause pain and tenderness in a "reference zone" remote from the stimulated point, either as a result of sympathetic overactivity, vasoconstriction and

ischemia, 858, 859 or of "some interference with innervation" of the nature of "partial nerve block." 1122, 1123 Consistent anatomic relationship between individual "trigger areas" and their "reference zones" existed, 2109 but "trigger areas" were reported in the neck and shoulder muscles of a high percentage of symptom-free individuals. 1050 It was proposed that latent "trigger areas" were clinically activated by trauma, overexertion, infection, chilling, visceral lesions, emotional stress and other factors. Advocated treatments included ethyl chloride spray, injection of local anesthetic 1119, 1121, 2109 or hydrocortisone, 454, 820, 1137 paravertebral block, 858, 859 oral hydrocortisone, 1559 an oral preparation of mephenesin, nicotinic acid and belladonna, 662 microwave diathermy, massage, exercises 1169 and ultrasonic therapy. 1060 [Recommended treatments are still too often based on conjecture and unconfirmed theory.—Ed.]

FIBROSITIS

The existence of a definable entity which could justify "fibrositis" as a specific diagnosis was questioned by many. "The most remarkable trend in soft tissue rheumatism in recent years has been the rejection of the concept of fibrositis first propounded by Gowers and later elaborated by Stockman. The critical examination of fibrositis has led it to totter and then to crumble." It was "a term used for many years as a diagnosis of convenience which permits the physician to tell the patient 'You don't have arthritis.'" 206 It had become "a phantom disease, a veritable depot for numerous varieties of soft-tissue rheumatism." 826, 827 Taverner expressed the opinion of many, as follows: "The concept of fibrositis, so popular 20 years ago, is now almost universally suspected and few would claim that any sound basis for it has been discovered." 2067

Fibrositis was defined as "a term, not a diagnosis, to describe the symptoms of aching muscles, soreness and stiffness, local tenderness and trigger points in fascial planes, sheaths of muscles and nerves, ligaments, tendons, periosteum and subcutaneous tissues." ¹²¹ Accumulated experience indicated that many cases of so-called "primary fibrositis" were in fact secondary to underlying diseases such as rheumatoid and degenerative arthritis, disc lesions, the "collagen diseases" and other definable entities. ^{121, 1111, 2071} Though fibrositis was often called "the most common form of acute and chronic rheumatism," a valid estimate of its incidence was impossible: "apparently no two physicians have the same criteria for diagnosis." ^{826, 827}

In an intriguing review of the "mythology of fibrositis," Kellgren 1111 described theories of etiology and pathogenesis which have failed to survive critical evaluation. Among these were Gowers' and Stockman's concept of "inflammation of white fibrous tissue," the once-popular fibrositic nodule, and "muskelhärten" of the Scandinavian and German groups, the theory of interstitial neuritis with segmental pain, and the more recent "mythology which has sprung up about trigger-points and vicious cycle pain mechanisms caused by reflex disturbances in sympathetic pathways." Nevertheless, fibrositis was still described as an inflammatory reaction in fibrous connective tissue, 521, 602, 1029, 2077 and the causative role of focal sepsis was revived. Below Fibrositic pain was regarded as one of the "reference phenomena" of the "myalgic spot." 858, 859, 1119, 1521, 1989 The role of psychic and emotional stress and tension was emphasized, 806, 826, 827, 2102 but rejected by one. 1119, 1121 Electromyographic studies confirmed

the correlation between measurable muscle tension and emotional states of anxiety, hostility and depression. 1805, 1877 Another study indicated that muscular tension reduced muscular blood flow during the period of contraction; the resulting ischemia caused a shift of potassium across the cell membrane, producing muscle pain, tenderness and fatigue. It was postulated that the potassium so released was Lewis' "P-factor" or one of its important constituents. 147 It was remarked that the fibrositis syndrome could have a variety of different causes, 121, 826, 827, 1111 and might be aggravated by trauma, mechanical and postural strain, infection, chilling, endocrine and metabolic disorders, and the patient's constitutional habitus. 858, 859, 1028, 1521, 2077 [Evidence incriminating some of these factors and the mechanism by which they produce symptoms is certainly obscure.—Ed.]

The typical symptom-complex of fibrositis has been described at length in previous reviews. "Cervical fibrositis" was frequently accompanied by headache and occasionally by earache, blurred vision and tinnitus.¹¹⁷¹ There were frequently no abnormal physical, x-ray or laboratory findings, even though there was limitation of movement, local spasm or generalized muscle tension and tenderness.^{121, 396, 826, 827, 1028} Muscle spasm as a cause of pain was examined by electromyographic technics; little reliable evidence was found to support the theory that muscle spasm is a direct cause of somatic pain.²⁰⁶⁷ "Trigger-points" were considered to be an integral feature of the syndrome by some, and palpable, tender "fibrositic nodules" were again described.^{821, 1171, 2077} Others considered that such nodules had a mere "mythical existence,¹¹¹¹ and were "only accessible to the finger of faith." ^{826, 827}

The difficulty of differentiating fibrositis from underlying structural diseases such as rheumatoid arthritis, disc lesions, degenerative joint disease and the "collagen diseases" was stressed; early stages of these conditions might present typical fibrositic symptoms before their true nature became evident. If the diagnosis of fibrositis was used to include a wide variety of unrelated disorders, many of which are definable as individual entities (such as bursitis, tendinitis, Dupuytren's contracture, subfascial fat herniation and the like), it had little more value than did its predecessor, "rheumatism." 829, 827 Terminology such as "myodysneuria," 859 "fibropathic syndrome," 1520, 1521 "pseudofibrositis" 920 or any other alias only further beclouded an already con-

fused subject.

Physicians should "inquire not only as to what kind of sickness has this man, but also what kind of man has this sickness" and should "deal with the person as well as the pain, his tensions, fears and anxieties." Explanation of the nature of symptoms and reassurance concerning the absence of serious crippling disease were recommended as the basic approach to treatment. A sensible balance between rest and normal activity, and correction of such factors as obesity, postural faults and occupational strain, were also advocated. Symptomatic therapy included non-narcotic analgesics, mild sedation, heat, massage and exercises. 121, 396, 826, 827, 1028, 1472, 2071 In one study, salicylate-succinate combinations were said to be superior to aspirin. 280 [This has not been confirmed.—Ed.] Short wave or microwave diathermy 1171, 1189 and ultrasonic therapy 726, 767 were useful in some cases. Good results from phenylbutazone were reported. 1119, 1121 Procaine infiltration of "trigger-points" retained its staunch advocates. 521, 820, 858, 859, 1028, 1119, 1121, 1520, 2077 Results of hydrocortisone injection were not striking. 1802 Therapy of dubious value and rationale included intracutaneous histamine, 1812 intradermal procaine, 425 mephenesin in combination with nicotinic acid and belladonna, 602 and with glutamic acid hydrochloride, 730 paravertebral block, 808 desensitizing injections of streptococcal extracts, 1929 and removal of foci of infection. 1882

DISORDERS OF FATTY TISSUE

Panniculitis. Baker 80 again described a syndrome, in menopausal females, of rapid gain in weight, pain, tenderness, paresthesias and easy bruising in patchy areas of the limbs and trunk. It appeared to be similar to conditions termed "juxta-articular adiposus dolorosa," "painful peri-articular fat pads" and "menopausal arthralgia." The reticular layer of the dermis showed increased density and thickening of collagen fibers, and the panniculus adiposus was normal, showing no inflammatory reaction. The term "panniculitis" was thus a misnomer. There was no significant difference in the electron-microscopic appearance of the collagen in affected and normal areas. Weight reduction, analgesics, sodium restriction, general exercises and small doses of thyroid were recommended treatment. Phenylbutazone was useful if it did not result in fluid retention. Estrogens were of theoretic value only. Ultimately complete, spontaneous recovery was the rule.

Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease). Some considered this disease to be a local allergic response of adipose tissue to a wide variety of allergenic factors, bacterial and otherwise. 461, 929 Streptococcal sensitivity was implicated in one patient with other allergic manifestations by eosinophilia in blood films and biopsy sections of affected tissues and by a consistently high antistreptolysin titer. 57 Serum lipase elevation was proposed as a possible etiologic agent, the released and activated enzyme acting secondarily on traumatized fat tissue. 1644 [No evidence was offered to support this theory, and the accompanying case report contained no mention of the patient's serum lipase level.—Ed.] A directly opposed theory implicated a lack of tissue lipase, interfering with conversion of nutritional fat to normal depot fat.57 Hyperglobulinemia and false-positive serologic reaction noted in another patient were interpreted as indicative of a fundamental relationship to the "collagen diseases." 2178 Death occurred in two patients, one of whom showed fatty infiltration, hemorrhage and necrosis of the liver. 929 Some reported striking benefit from cortisone and ACTH, 840, 461 but in others these hormones provided only slight symptomatic relief, without significant alteration of the disease

PSYCHOGENIC RHEUMATISM

plete remission after roentgen radiation of affected areas. 1816

process. One patient who derived no benefit from cortisone experienced com-

Psychogenic rheumatism, defined as the musculoskeletal expression of tension states or psychoneuroses, accounted for as many as 40% of patients attending some rheumatic disease services, though a much smaller percentage in others. Ten to 20% of cases of back pain were said to be psychogenic in origin. Psychogenic rheumatism could occur in "pure" form, or as a functional overlay of minor organic disorders, or as the perpetuation of symptoms of a previous organic illness, long past and gone. Patients were usually tense, anxious, vigilantly hostile and resentful, with deep-seated feelings of being hurt by life. Their resentment, often subconscious, found expression in bodily symptoms as a defense against emotional conflicts. Suppressed urges to express this resentment in motor aggression resulted in sustained muscle tension and the other features of this syndrome. The constant state of physiologic prepared-

ness for danger and aggression was associated with excessive perspiration, cold extremities and other manifestations of disturbed autonomic function. 1250 Correlation of electromyographically measured muscle tension with psychodynamic themes, particularly those of anxiety, hostility and resentment, was confirmed in two well documented studies. There was suggestive evidence that, to a degree, the subject matter of these emotional themes influenced the anatomic sites where increases in muscle tension occurred. 1805, 1877 In another study of muscle spasm as a cause of pain, spontaneous electric activity was found to be a common electromyographic finding and was seldom associated with pain. 2067

Lengthy, vague and often irrelevant histories, pain, muscle cramps, spasmodic contractions, especially on dropping off to sleep, paresthesias, sweating and fatigue were characteristic features. The graphically described pain, frequently generalized but at times localized, particularly in the back, neck and shoulder areas, was commonly migratory and influenced little or not at all by aspirin, heat, activity, position or external environment. Headache was a frequent accompaniment. Some but not all patients described a parallel between these symptoms and their emotional state. Objective findings included diffuse muscle tension and tenderness, hyperreflexia, tremors, flinching on examination, exaggerated posturing, bizarre movements and gait, limited movement, excessive perspiration and cold extremities. Not infrequently the syndrome closely simulated that of "fibrositis." 694, 826, 827, 1250, 1309, 2072, 2192

It was recommended that, in the absence of demonstrable organic cause of symptoms, diagnosis should be based on positive factors revealed by a searching history and personality study. Careful, complete investigation at the initial consultation was advocated; later, repeated examinations would merely fix the patient's conviction of organic disease. At the same time, "the red herring of emotional conflict which can be found in anybody" should not mislead the physician or permit an inadequate investigation which could fail to disclose occasional cases of serious organic disease, 2040 Comparison of the effects of cutaneous and deep infiltration of painful areas with procaine and with a saline placebo occasionally aided in the differentiation of psychogenic from organic pain and hyperesthesia.2002

Treatment was often difficult and time-consuming, beginning with establishment of a firm diagnosis without unnecessary delay, explanation of the nature of the symptoms, and strong reassurance concerning the absence of disease. Emotional conflicts should, if possible, be brought to light and discussed realistically. Psychotherapy should not be pushed too rapidly. Patients with deepseated, fixed psychoneuroses might require specialized psychiatric care. If drugs or physical therapy were used, the patient should be convinced that these were not a treatment of disease but were employed solely to provide symptomatic relief. 694, 1028, 1309, 2072, 2192 Chlorpromazine, 1250 reserpine 108 and suggestion therapy by placebo injections 2002 might sometimes be helpful. Some patients with "tension neck syndrome" were relieved by microwave diathermy, massage, exercises and cervical traction. 1160, 1171

TUMORS OF SYNOVIAL TISSUE

Punch biopsy by means of a specially designed instrument was advocated as a useful, relatively simple and safe procedure to aid in the diagnosis of tumors and other disorders of synovial tissue. 1640 Rarely, Hodgkin's disease had chronic hydroarthrosis as the presenting symptom; one such case was reported. 1254

Hemangiomas. Discrete or diffuse hemangiomas occurred most frequently in large joints, particularly the knee, rarely in tendon sheaths, and not at all in bursae. Multiple calcified phleboliths were occasionally observed in the surrounding soft tissues. 118, 1285 The first instance of cavernous hemangioma of the knee associated with synovial chondromatosis was reported. 1801

Osteochondromatosis and Synovial Chondromatosis. These disorders were considered to result from an irregular, self-limiting process of metaplasia arising at multiple sites in the synovialis of the knee, and less commonly in other joints, bursae or tendon sheaths. The process usually remained monarticular. The younger age groups were predominantly affected. Pathologically the synovialis showed multiple cartilaginous foci, many of which later became ossified, developed tenuous pedicles or extruded into the synovial cavity. Their growth potential tended to be self-limited; spontaneous regression frequently occurred. [This seems unlikely.—Ed.] X-rays appeared normal until the chondromas ossified. At times, constant mechanical trauma to joint surfaces led to severe secondary degenerative changes in affected joints. Synovectomy was the treatment of choice. As many as 439 osteochondromas were removed from the knee of one patient.

Pigmented Villonodular Synovitis. The etiology remained controversial. [See Experimental Arthritis.—Ed.] The basic pathology was considered by some to be identical with that of giant cell synovial tumor, xanthoma, xanthogranuloma, myeloplaxoma and benign synovioma. The morphology and cytology of these lesions varied with their site of origin, degree of localization and stage of development. The diffuse villonodular form involved spacious joint cavities, particularly the knee, while localized nodules occurred in the confined tendon sheath spaces, mainly in the hand. Clinical, radiologic and pathologic features were reviewed. Treatment consisted of removing as much as possible of affected synovialis, and subsequent radiation. P. 1265, 1886, 2270 Additional case histories were reported. In two instances the lesion arising from the hip extended retroperitoneally and produced an abdominal mass resembling a psoas abscess. Pour additional cases with hip joint involvement were reported. To the diffusion of the second of the second

Giant-Cell Tumor of Tendon Sheaths. That these tumors represent the same basic pathologic process as that of pigmented villonodular synovitis was reëmphasized. 1265 Of 104 giant-cell synovial tumors in one series, 70% involved sheaths in the fingers. One apparently arose from the temporomandibular joint. 1357 Another report of five "giant-cell tendon sheath tumors" did not clarify whether some or all of these were not actually synovial sarcomas. 2

Multiple Reticulo-Histiocytosis of Synovia and Skin. Possibly related to, but in certain features distinct from, benign synovial tumors, xanthomatosis, and the reticuloendothelioses was this rare disorder of unknown etiology and characterized by multiple skin papules, acute polyarthritis and tenosynovitis. Both skin and synovial lesions showed a granulomatous reaction featured by multiple histiocytes and histiocytic giant-cells.⁸¹¹

Synovial Sarcoma. Clinical, radiologic and pathologic features were reviewed and additional case histories recorded.^{3, 447, 508, 1265, 2138} Unusual sites of this tumor reported in one series were the sternoclavicular joint and the larynx.¹³⁵⁷ Metaplasia of primitive cells within bone, with formation of synovial tissue and malignant transformation, was postulated as the mode of development of three so-called "adamantinomas of the tibia," ^{957, 1226} and of a unique malignant tumor of the middle phalanx of a finger.¹⁶⁶¹ These tumors were all considered to be synovial sarcomas arising within bone.

Treatment of synovial sarcoma continued to show disappointing results. Primary amputation was recommended, as was block dissection of the tumor and regional nodes, followed by radiation. One patient treated with large doses of roentgen therapy only was apparently free of recurrence four years later.⁸⁰⁰ Of 37 patients followed for more than five years after treatment, 29 had died of the tumor; ¹⁸⁷² of 24 patients, 19 had either died of the tumor or had had definite recurrences in less than 10 years.⁴⁴⁷ An unusual instance of survival for more than 23 years after diagnosis was reported in one case.⁸⁴⁶ Though nearly all synovial malignancies were synovial sarcomas, a rare chondrosarcoma of the temporomandibular joint was reported.⁷⁸⁶

ARTICULAR DISEASE ASSOCIATED WITH PRIMARY BONE PATHOLOGY

Clubbing of the Fingers and Hypertrophic Osteoarthropathy. It was emphasized that the two hereditary-familial conditions, congenital clubbing and idiopathic hypertrophic osteoarthropathy, were entirely different from acquired clubbing and generalized hypertrophic osteoarthropathy, sometimes termed "pulmonary" osteoarthropathy. The first two were of little clinical importance, whereas the last two were of real diagnostic significance and, in addition, the osteoarticular manifestations might be of such severity as to incapacitate the patient.²¹⁴⁰

Generalized hypertrophic osteoarthropathy was considered to be a more advanced stage of acquired clubbing of the fingers. 587, 1877, 2146 Either might occur independently, but hypertrophic osteoarthropathy with periosteal bone proliferation, which usually appears later, might sometimes precede clubbing. 1870, 2020, 2146, 2214 Either could be the initial manifestation of serious pulmonary disease, although respiratory symptoms often do not appear until months later. Early diagnosis of a tumor, subacute bacterial endocarditis or other serious disease sometimes depended upon recognition of these conditions. 784, 2146 The triad of clubbing, periostitis and synovitis associated with chronic chest disease has been referred to as "pulmonary osteoarthropathy." Periosteal or synovial changes did not suddenly develop after stationary asymptomatic clubbing had been present for years. 2146

All 24 patients with generalized hypertrophic osteoarthropathy associated with bronchial carcinoma had experienced "rheumatic" symptoms, and 16 had had joint disability as the first evidence of disease. Five of seven other patients with intrathoracic malignancies had symptoms referable to the extremities as their initial complaint. Hypertrophic osteoarthropathy was observed in 61 of 1,024 patients (6%) in whom pulmonary resection was performed. Fifty-five of the 61 had some digital clubbing, and it was present in every case of pulmonary suppuration. Joint pain was almost always due to pleural mesothelioma or carcinoma of the lung, but did not occur in a single patient with tuberculosis or pulmonary suppuration. Of the 481 patients in this group with malignant tumors, 25 (5.2%) had articular manifestations or hypertrophic osteoarthropathy; 23 of the 25 had clubbing of the fingers, and nine also had painful joints. Painful joints associated with hypertrophic arthritis frequently accompany intrathoracic malignancies.—Ed.]

Clinical Data. Pain was reported to be an unusual symptom in finger clubbing. Soft tissue proliferation at the base of the nail distorted the finger tip to varying degrees, depending on anatomic peculiarities and the rapidity and degree of change. The nail root was elevated, with loss of the angle at the base

and the nail curved to conform to the bed. Periungual erythema and ridging of the nail in its long axis as well as convexity in both axes were seen. The process might be symmetric or asymmetric, and involve all or only one digit. 784 Critical study of the validity of the physical sign of clubbed fingers suggested that it was often unreliable.1871 Proliferative periostitis as it develops in hypertrophic osteoarthropathy was shown to be characterized by lymphocytic and round cell infiltration, and by subperiosteal formation of a new bone pseudocortex from 1 to 5 mm. thick which ultimately fused with and expanded the cortex of the affected bone. The lower end of the long bones of the forearms and legs, metacarpals and metatarsals were most commonly affected, although clavicles, ribs, pelvic bones, scapulae and malar bones were sometimes involved when the process was extreme. Adjacent joints were reported to show extra-articular thickening, chronic synovitis, nonspecific cartilage changes, osteoporosis and, in extreme cases, deformities and subluxations. 1870 Radiologically demonstrable periosteal proliferation of long bones was at times asymptomatic. Permanent clubbing was said to exist as a distinct entity, with no tendency to progress to the "pulmonary" type of osteoarthropathy just described.2146 The periosteal proliferative reaction was more likely to occur with a localized pulmonary lesion such as a carcinoma, to affect larger joints and to appear and disappear rapidly. Acquired clubbing was often associated with diffuse pulmonary disease and developed more slowly. 186, 1669, 1870, 2214

It was again noted that articular symptoms of effusions, stiffness, pain, tenderness and limitation of motion could be severe and as disabling as progressive rheumatoid arthritis. Deep pain of a burning character aggravated by dependency of the extremity might be distressing. X-ray evidence of subperiosteal bone formation adjacent to the affected joints was usually present. Clubbing of the fingers might precede, accompany or follow this process. The extremities were often shiny, red, perspiring and edematous, and the long bones might be very tender on palpation. Subsidence of the symptoms and regression of the findings occurred in a high percentage of cases within a short time after the underlying lesion was removed. Recurrence of the malignancy was frequently associated with recurrence of the pain, with or without a return of the osteoarthropathy.⁵⁸⁷, ⁸⁹⁴, ¹⁸⁷⁷, ¹⁸⁷⁰, ²¹⁴⁶, ²²¹⁴, ²¹⁶⁶

Hypertrophic osteoarthropathy was associated with chronic pulmonary infections, intrathoracic malignancies, congenital heart disease, arteriovenous aneurysm of the lung, benign tumor of the chest wall, carcinoma of the nasopharynx, myeloid leukemia, ulcerative colitis, steatorrhea, liver disease, hypothyroidism following thyroidectomy, polycythemia, syringomyelia, Raynaud's disease, scleroderma and acrocyanosis.^{186, 387, 1600, 1870, 2020, 2146}

Acromegalic-like features were mentioned by several. 186, 1877, 1870, 2198 In one patient these consisted of a coarse, furrowed facial appearance, spadelike hands and hyperkeratosis of the palms and soles. This patient also had generalized hypertrophic osteoarthropathy and gynecomastia in association with a right upper lobe opacity. 186 Acromegalic features, with or without gynecomastia, when associated with articular symptoms, suggested a pulmonary malignancy. 2196

Atypical clubbing of the fingers, an unusual finding in primary hyperparathyroidism, was reported in one of two sisters with this condition. Another patient with classic severe "osteitis fibrosa cystica generalisata" had clubbing of the fingers and marked nail deformity. X-rays showed the terminal phalanges to be almost completely absorbed. Following removal of a parathyroid ade-

noma the terminal phalanges recalcified, but appeared to be shorter and broader than normal phalanges and were also blunted at the distal end. Unilateral clubbing of fingers of the left hand of a five year old girl who had absence of the aortic arch was reported. Unidigital clubbing of the left index finger of an 11 year old girl was apparently idiopathic in nature. Increased length of the terminal phalanx was an unusual feature.

Pathogenesis. The cause remained unknown. No one hypothesis was satisfactory. The high incidence of peripheral pulmonary lesions suggested that the pluripotential mesothelial cells of the pleura might release some osteoblast-stimulating substance that could induce the articular and bony response.²²¹⁴ Theories of toxemia, anoxemia, capillary stasis and lymph stasis were again reviewed. 587, 1377, 1870, 2146, 2196 Increased peripheral blood flow was known to occur, as measurements have shown that it was a constant feature and one which disappeared within two or three hours after removal of a lung tumor. The reason for this was unknown. Hypotheses of disturbance of endocrine balance, tumor secretion and autonomic-systemic vascular reflex were examined in the light of information on the effect on osteoarthropathy of resection of the tumor, ligation of the pulmonary artery on the affected side, and denervation of the hilum on the same side. All three hypotheses had defects. 1870 Reflex stimulation in the autonomic nervous system is possibly the best lead at present. Local disturbances such as occurred in the shoulder-hand syndrome could result.2196 The reported improvement following vagus nerve resection might be explained on some such basis.887

Idiopathic Type. Little was written about this chronic, self-limited condition, said to occur predominantly in males. Pain, swelling, stiffness and enlargement of joints, soft tissue edema, thickening of the subcutaneous tissues, clubbing of the fingers, evidence of vasolability, thickening of the skin, gynecomastia, striae, feminine distribution of hair, acne vulgaris and hypertrophy or atrophy of the ungual tufts of the fingers became manifest in adolescence, increased into adult life, and finally reached a standstill with intermittent relapses. The characteristic roentgenographic finding was proliferation of the periosteum of long bones. This commenced in the distal portion and eventually involved the entire shaft. It could not be differentiated by x-ray from secondary osteoarthropathy. Absence of demonstrable causative disease, onset at puberty and the long course led to a diagnosis of the idiopathic form. It was differentiated from acromegaly, Paget's disease, syphilitic periostitis and hereditary osteoarthropathy. Etiology remained unknown. The diagnosis had to be made with caution and only after every possible primary etiologic factor had been considered. A report appeared of a single case at one time mistakenly considered to have rheumatoid arthritis because of recurrent enlargement and effusions of the knees and ankles.1097

Sarcoidosis. No new information concerning the bone or joint lesions of sarcoidosis appeared. The trend in recent years has been toward broadening the diagnostic base of this entity. The trend in recent years has been toward broadening the diagnostic base of this entity. The trend in recent years has been toward broadening the diagnostic base of this entity. The trend is reason, it might be worth while to repeat the definition offered by the Conference on Sarcoidosis convened by the National Research Council in 1948: "Sarcoidosis is a disease of unknown etiology, characterized pathologically by epithelioid tubercles, with inconspicuous or no necrosis, occurring in any organ or tissue, and by the frequent presence of refractile or apparently calcified bodies in the giant cells of the tubercles. The lesions may be replaced by fibrosis, hyalinization, or both. Clinically the lesions may be widely disseminated. The tissues most frequently involved are lymph nodes, lungs, skin, eyes and bones (especially of the extremities). The clinical

course is usually chronic with minimal or no symptoms. However, there may be acute phases, characterized by malaise and fever. There may be symptoms referable to the tissues and organs involved. The tuberculin test is frequently negative. Plasma globulin is often increased. The outcome may be clinical recovery without gross or radiologically visible residuals, or it may be impairment of the functions of the organs involved, or a continuous chronic course of the disease." ¹

Incidence. In the United States, sarcoidosis was more frequent in the Negro population. It was quite common among the Scandinavians, and one series of 90 white patients was reported from England. 443, 679, 760 The epidemiology of the 350 recognized cases of sarcoidosis in the American Armed Forces in World War II was investigated recently. Of this group, 334 were still living. The highest incidence was found in the southeastern United States, in the "below fall line" area. Ratio of Negro to white cases of 18:1 did not entirely account for this geographic distribution. Meteorologic conditions, distribution of plant and animal life, agricultural practices and over-all population densities were not overtly associated with distribution of cases. Since the fall line delineates the boundaries of geologic formations, investigation of major soil groups was carried out. It was suggested that the beryllium content or crystalline material in the soil might be significant factors. Fine, sandy soil with a high percentage of silica was found in areas with a high incidence of sarcoidosis. Residence in a rural area favored development of the disease. 760 The geographic distribution of the 177 sarcoidosis patients seen at the Mayo Clinic from 1940 through 1951 was the same as that of the total clinic registration. There was no predominance from the southeastern part of the United States.341

Sarcoidosis occurred in a brother and sister aged 48 and 33 years, respectively. There was a four-year interval between the apparent onset in each; the clinical and x-ray features were similar. Osseous lesions of the phalanges were present in one,

while the other had no demonstrable lesions of the bones of the hands. 2052

Clinical and Pathologic Data. A number of case reports and several reviews appeared. 86, 448, 679, 992,1151, 1324, 1445, 1597, 1607, 1706, 1922, 2262 In 90 patients the presenting symptoms, in order of frequency, were chest symptoms of pain, cough and dyspnea, lymph node enlargement, malaise, skin manifestations, weight loss, nasal obstruction, dysphagia, salivary gland enlargement, abdominal pain and visual disturbances. Less frequent presenting features included swelling of a finger in two patients, large joint swelling in two, swelling of the lacrimal gland, nodules on a tendon sheath, symptoms of diabetes insipidus and jaundice in one each. "In a few sites the clinical features of the disease are characteristic, in some suggestive, while in others they offer no assistance."

Pulmonary sarcoidosis most often affected the general health of patients. Many with extensive lung involvement were asymptomatic. A minority, particularly those with progressive lesions, had fever, night sweats and weight loss. Hilar and paratracheal lymphadenopathy usually regressed, but in some persisted as the pulmonary lesions progressed. Serious effects of pulmonary lesions followed scarring when pulmonary fibrosis with emphysema or bronchiectasis led to right heart failure. This was the most common cause of death attributable to sarcoidosis. The pericardium as well as the myocardium was sometimes directly involved by granulomatous tissue. Tachycardia and arrhythmias were often seen. 468, 1445

In one series of 21 proved cases of sarcoidosis, bilateral hilar adenopathy was present alone in five and with right paratracheal adenopathy in 10.679 Bilateral hilar lymphadenopathy was accompanied by erythema nodosum in 12 of 17 patients, and seven of these also had polyarthritis.²²⁶² [Details of the arthritis were not given.—Ed.] Two other patients in whom positive Kveim tests were reported had fever,

erythema nodosum, iritis and arthritis. Their joints were stiff, painful, tender and slightly swollen. Salicylate therapy was ineffective. Mantoux reactions were negative to a dilution of 1:100.1029

Instances of sarcoidosis of the bones and joints were mentioned infrequently. Characteristic roentgenographic defects in the hands and feet were reported in 17.3% of 77 patients in one series.¹⁰¹¹ Bones were involved in only five of another series of 90 patients. One of these patients, who had injured his knee 10 years before, died of a pulmonary embolus three weeks after synovectomy of this joint. No evidence of sarcoidosis was found in the excised synovia, though at autopsy other organs were found to be extensively involved.⁴⁴³ The typical lesions of the hands and feet were punched-out areas in the medullary portion of the phalanges, metacarpals and metatarsals, without periosteal involvement.^{1445, 1807} Biopsy of the gastroenemius muscle was of value principally in patients with arthritic manifestations.¹⁰¹¹

A 22 year old woman with bilateral hilar adenopathy and pulmonary parenchymal lesions, splenomegaly and lymphadenopathy showed marked regression of the hilar and pulmonary parenchymal lesions during the latter months of pregnancy, so that roentgenograms were virtually normal at delivery. However, postpartum x-rays showed a progressive return of these abnormalities. An anterior scalene fat pad biopsy eight months after delivery showed a lymph node with histologic characteristics of sarcoidosis. Whether regression was incidental to the cause of the disease or due to pregnancy could not be determined on the basis of this or the few other similar reports.¹⁷

A patient with generalized sarcoidosis had involvement of the gastric mucosa and submucosa, and a peptic ulcer, probably on this basis, was found on examination of the resected specimen.¹⁵⁹⁷ The first case of extensive peritoneal sarcoidosis was reported,¹⁷⁴⁹ as was another with intestinal sarcoidosis.¹⁸²⁴ Central nervous system sarcoidosis with lesions involving the left optic tract and the pyramidal tracts in one instance ⁹⁹² and the right temporal lobe and the sella turcica in another ¹⁹²² was reported. Binocular episcleral nodules, optic atrophy and unilateral calcareous cataracts were rare manifestations of sarcoidosis.¹¹⁸¹

Hypercalcemia of sarcoidosis studied in four patients showed fecal excretion of calcium to be less than normal. Following cortisone therapy, this returned to normal and the blood calcium fell to normal. Overabsorption of calcium from the bowel and excessive erosion of bone by sarcoid granulomas were probably both contributory.³⁶ Another case of sarcoidosis with hypercalcemia and renal impairment as well as calcium phosphate deposits in the conjunctiva was reported. This was further complicated by exposure to beryllium and the development of erythema nodosum on both legs. The response of hypercalcemia to cortisone was prompt.⁸⁷¹ Liver biopsy was found to be a safe and reliable procedure, as 59 of 93 patients with sarcoidosis had typical epithelioid cell follicles.¹⁸⁷² In another study, eight liver biopsies were done and all were positive.⁶⁷⁰

The Kveim reaction or test was studied by several groups. 1011, 1029, 1761, 1906 The differences of opinion concerning the value of this procedure were commented on as follows: "Until more rigid criteria for assessing the test are adhered to by all investigators there is apt to be continued disagreement as to the usefulness and specificity of the test." The papule at the site of the positive Kveim reaction was considered to be a lesion of sarcoidosis. 1761 Others were not so definite in their statements concerning the pathogenesis of the lesion, but felt the test provided diagnostic proof of sarcoidosis and an index of activity of the disease. 1029, 1906 It was also emphasized that the Kveim reaction deserved less use as a specific diagnostic measure but should be studied as an immunologic phenomenon. 1011 Patients with sarcoidosis produced significantly higher titers of iso-agglutinins in response to the intravenous administration of mismatched blood than did normal individuals or patients with tuberculosis.

This serologic hyperreactivity suggested that hypersensitivity might play a role in the pathogenesis of sarcoidosis. 1815

Etiology and Pathogenesis. The cause of sarcoidosis was unknown. 1010, 1091, No bacterial, viral or mycotic agent had been incriminated. Neither had sarcoidosis been shown to be one of the collagen diseases. 1010 Similarity between sarcoid and beryllium granulomas had been accepted by some as evidence that sarcoidosis was a hypersensitivity disease. 1091, 1761 Epithelioid cell tissue in sarcoidosis as well as in tuberculosis and "quartz sarcoid" contained appreciable amounts of phospholipid. An indirect epithelioid type of immunologic reaction may occur when the primary irritant is an antigen capable of producing antibodies containing or accumulating phospholipid. This was suspected of being the pathogenic basis of sarcoidosis. 1718 Electron-microscopic studies of erythrocytes from a patient with sarcoidosis showed spherical virus-like particles with irregular contours on or in the erythrocytes. These bodies were 240 to 250 millimicrons in diameter, resembled the virus of measles, and were not found in normal human blood prepared and examined in the same way. 1708 [This does not prove a virus etiology.—Ed.] Failure of activation of tuberculosis following adrenocorticotropin or cortisone therapy was cited as evidence that sarcoidosis was not a tuberculous infection. The absence of febrile relapses during or after cortisone therapy was also considered to be evidence against any other bacterial or fungal infection as a cause of sarcoidosis. 1010

The finding of sarcoid tubercles in isolated tissue did not necessarily establish the presence of systemic sarcoidosis, as a similar histologic picture occurred in some types of tuberculosis as well as in histoplasmosis and berylliosis. 1011 However, a positive or compatible biopsy of skin or lymph node, a positive or compatible liver biopsy or a properly carried out positive Kveim test was certainly of aid in making a diagnosis. 1029 Until the etiology was known, the diagnosis would depend upon a consistent histologic picture of organs or tissues characteristically affected, and exclusion of diseases which simulated sarcoidosis, especially tuberculosis, histoplasmosis and berylliosis. 1011

Treatment. Adrenocorticotropin and corticosteroids were of limited value, at least in the early stages in treatment of sarcoidosis; they did not cure the disease. Pulmonary sarcoidosis was not always benefited, but extrapulmonary lesions, especially those of the eye and parotid gland, often showed a striking response. 448, 810, 1009, 1010, 1090, 1151, 1445 Tuberculosis needed to be eliminated as a diagnostic possibility before adrenocorticotropin or corticosteroid therapy was started. 1010 Antituberculous therapy in conjunction with these agents was recommended by one author. 810 Temporary improvement during pregnancy was reported in one case. 17

Osteochondritis. Osteochondritis of Growth Centers (Epiphysitis). The use of various eponyms did not improve the understanding of this condition. The hip, knee, elbow and spine were most frequently affected. Osteochondritis of the hip appeared in identical male twins within a four-month period during their eighth year of life. Other members of their family had no epiphysial abnormalities. To Hereditary multiple epiphysial disturbance, a constitutional skeletal disease with onset between the ages of seven and 13 years, was again reported from Sweden; the trait was recessive, and parental consanguinity was established. This may be similar to the condition reported as "multiple epiphysial dysplasia." 1021

Hip. Involvement of the hip was referred to as Legg-Calvé-Perthes' disease, Legg-Perthes' disease, osteochondritis deformans, coxae juvenilis, coxa plana and pseudocoxalgia.^{672, 1080, 1017} Limp, muscle spasm, limitation of internal rotation and abduction, and sometimes shortening of the extremity constituted the physical findings. Pain varied in intensity. The femoral head showed degenerative changes, with roughening and flattening.^{672, 1080} The level of serum protein-bound iodine in 32 cases was found to be normal, and was presented as evidence against the often suspected hypothyroid basis for Legg-Perthes' disease.¹⁰⁹⁴

Direct observation of the joint during the active stages showed the capsule, synovialis and articular cartilage to be thickened. Edema and hyperemia of the synovialis were present at the time motion of the joint was markedly limited. Softening of the metaphysis adjacent to the epiphysial line was considered to be the result of increased vascularity. The femoral head, on inspection, usually appeared to be normal, though roentgenograms showed radiolucent areas, the site of fibrous tissue replacement of necrotic bone. Later, these fibrous areas were replaced by bone.⁶⁷²

Three stages of this condition could be established by roentgenograms. The first was characterized by increased thickening of the capsular shadow, widening of the joint space and decreased density of the metaphysis adjacent to the epiphysial line. The second stage, in addition, had increased density of part or all of the femoral head. The third stage was characterized by radiolucent areas, indicative of revitalization of the femoral head, and widening of the neck of the femur. Eventually there were flattening and widening of the femoral head. Fragmentation of the head often resulted in a corresponding change in the shape of the acetabulum. The deformed head might project beyond the acetabulum. 1030, 1036

Certain measurements of the roentgenographic shadows of the femoral head and neck and of the acetabulum of the involved and normal sides in cases of unilateral disease were reduced to a series of "epiphysial quotients" by which radiologic progress of the diseased hip was followed. Patients with unfavorable radiologic results were usually asymptomatic and were considered to have satisfactory clinical results. However, these poor radiologic results were unsatisfactory mechanically, and such inefficient joints could be expected to wear out more rapidly than would normal joints, and to cause trouble in later life. The acetabulum on the affected side was found to be elongated, though not necessarily deepened, in 82 unilateral cases examined following treatment. 657

In Finland a series of 33 patients with Legg-Calvé-Perthes' disease were regularly found on reëxamination 10 to 30 years after the diagnosis was first made to have changes in the shape of the femoral head and neck as well as in the acetabulum. In about 60% the head had assumed a mushroom-like or angular shape. The acetabulum conformed except when the head was markedly deformed. Mobility of the hip was reduced in nearly all.¹⁶¹⁷

Treatment aimed at prevention of femoral head deformity revolved about maintenance of full joint motion, a strict regimen of nonweight-bearing, and relief from muscle spasm, best accomplished by traction. A nonweight-bearing splint was recommended for use later.⁶⁷² Reconstructive surgery for correction of hypertrophic changes involving the femoral head was often necessary in later life.¹⁰³⁰ Twenty-five children with Legg-Calvé-Perthes' disease given a dose of 50 mg. of Aureomycin daily were said to have accelerated growth and accelerated reossification of their epiphyses or growth centers.⁷⁹⁸

Knee. Osgood-Schlatter disease, or osteochondritis of the growth center of the anterior tibial tubercle, occurred most often in adolescent males and was frequently bilateral. Controversy still existed as to its exact nature. Swelling and tenderness of the tibial tubercle and the distal end of the parapatellar tendon, with pain over the anterior aspect of the knee, were the usual findings. Roentgenograms showed thick-

ening of the tendon and soft tissues anterior to the tibial tubercle, and calcification in the substance of the patellar tendon in some cases. This self-limiting process might persist from a few months to two or three years. The diagnosis in older individuals was made on the basis of symptoms and roentgenograms. Thirty patients with 39 lesions of the anterior tibial tubercle were treated in a one-year period in a single military hospital. Ages varied from 12 to 36 years, with an average of 23 years. On the basis of observations made during surgical exploration of the knees of 15 patients, the authors concluded that trauma with secondary ossification within the infrapatellar tendon was the cause of this syndrome. Treatment was conservative, 506 though surgical removal of the intratendinous ossicle might become necessary in those patients having persistent pain. 2080

Previously unreported osteochondritis of the superior tibial epiphysis was reported as occurring in a 12 year old boy.²¹⁷ Osteochondritis and chondro-epiphysitis involving the long bones of all four extremities were found on roentgenograms of an infant with congenital syphilis.¹⁸⁵⁸ [Osteochondritis of the spine is discussed in the section on Backache.—Ed.]

Osteochondritis Dissecans. This has been described as a noninfectious aseptic necrosis of a segment of subchondral bone, often—though not always—resulting in an osteocartilaginous sequestrum in the affected joint. The lateral aspect of the medial femoral condyle, the capitellum of the humerus and the talus were most frequently affected. Symptoms were intermittent as long as the fragment was embedded. When it was sequestrated, pain and "locking," with effusion into the joint, often occurred. 506, 796, 1030

The pathology and x-ray findings correlated well. The embedded fragment located near the joint surface showed up as an area of increased density surrounded by a narrow zone of decreased density. Displacement of the fragment resulted in the appearance of a loose body in the joint and a corresponding defect in the articular surface. Later, this loose body was noted to be decalcified as it became cartilaginous, and also the outline of the defect became less distinct as it filled in. 796

A patient with osteochondritis dissecans of the lateral condyles of both tibiae was reported. The Chondromalacia of the patella was essentially a cartilaginous degeneration, and was interpreted as entirely different from osteochondritis dissecans, which affected bone primarily and the overlying cartilage secondarily. The Osteochondritis dissecans of the supratrochlear septum was reported as a cause of loose bodies in the elbow. The Osteochondritis dissecans of the supratrochlear septum was reported as a cause of loose bodies in the elbow. The Osteochondritis of the elbow joint was described, but gave no positive information in patients with osteochondritis or epicondylitis.

A group of 10 cases of osteochondritis dissecans occurred within a short time at a military training center following ankle injuries which resulted from a running jump off a ramp to hard-packed earth about 10 feet below. Heavier men from non-strenuous premilitary occupations seemed susceptible to these "flake fractures" of the talus. They were considered to have sustained severe ankle sprains when examined immediately following injury. Aseptic necrosis of separated bone fragments occurred in every case of "flake fracture" of the talus in this series. Small impactions or "flake fractures" were sometimes not detectable for 10 days, by which time calcium absorption along the line of crushed and broken trabeculae had taken place. Recurrence of pain following a relatively asymptomatic period of two or three months after this severe "sprain" was the usual history. Osteochondritis dissecans could be detected by x-ray before traumatic arthrosis developed. 404

Etiology and pathogenesis of osteochondritis dissecans were reviewed. Multiple slight injuries, or a major trauma by damaging the vascular supply, was considered to be of importance in the development of bone necrosis. 494, 506, 786, 951, 1030, 1211 Some believed there was a familial factor or a constitutional predisposition to the disease and that trauma acted as the precipitating cause. 786, 1628, 1728 Osteochondritis dis-

secans in both knees of two brothers and in one knee of their sister was reported. 748 In another family the mother and three of her four daughters had bilateral involvement of either the knees or the elbows. 1628 On the basis of x-rays and tissues, Ribbing concluded that the etiology was complex, and that both trauma and a constitutional tendency were factors. He found that an accessory bone nucleus became detached in childhood, and during adolescence fused into adjacent cancellous bone, being partly separated from this bone by islands and strands of preëxisting cartilage. The vascular supply of the bone nucleus from its previous connection was incomplete and from adjacent tissue inadequate. Mild injury or strain produced slight dislocation, with serious effect on the blood supply of the bone nucleus, which led to bone necrosis. 1728 In an experimental study a fragment of cartilage was gouged from a medial condyle of each of 12 young rabbits. This was then replaced in the defect of the condyle, to which it remained attached by a strand of synovialis membrane. Roentgenograms taken 33 to 116 days later showed loose bodies similar to those found in human osteochondritis dissecans in eight animals. This suggested to the author that cartilage fracture in early childhood might possibly give rise to an osteochondritis dissecans which manifests itself years later. 1211 Conservative management, such as a plaster cylinder applied to the knee, was used successfully in 11 children in whom the fragment had not yet separated. Loose fragments needed to be removed. 506

Several examples of multiple epiphysial dysplasia, including four in one family, were described. This developmental entity was characterized by generalized symmetric disorganization of developing epiphyses. In time the epiphyses tended to consolidate, so that after puberty the bones were well formed and the joints functioned well, although deformities such as angulation of the knee joint persisted, and faulty mechanics later could cause degenerative joint disease. Patients did not grow

beyond five feet (152 cm.) in height. 1021

Other Conditions. Studies of two patients with an unusual, progressive osteolytic process termed massive osteolysis were reported. 816 Other names applied to this syndrome included acute spontaneous absorption of bone, phantom bone and disappearing bone. The striking x-ray findings were unexpected and surprising. It was questionable whether trauma was more than a complication of preëxisting disease. The osteolysis was not limited to one bone but involved the clavicle, scapula, ribs, sternum, humerus, radius, ulna, jaw, bones of the hands or feet, femur or pelvis. Both cortical and cancellous elements of bone were progressively affected. The process stabilized at times, but usually continued until only a fibrous band, probably periosteum, was left. In all cases where biopsy specimens were obtained, an overgrowth of small, thin-walled vessels, a form of angiomatosis affecting the bones and surrounding tissues, was found. Generally these were of blood vessel origin. None of the angiomatous changes was considered to be malignant; it was even doubted that they were neoplastic. Disturbances in osteoblast-osteoclast activity, or acute inflammatory reactions with secondary fibrosis and trophic disturbances, were other etiologic processes considered. The term "hemangiomatosis" was proposed to describe the proliferative process.817, 818

Cupping and fraying of the outer ends of the clavicles due to resorption of bone were associated with proved secondary hyperparathyroidism. Pseudocysts adjacent to joint spaces did not involve them. The parathyroids were markedly enlarged; the right kidney was rudimentary, while the left showed far advanced

pyelonephritis. 720

Arthropathy of acromegaly was again reported. 680, 956, 1077 In acromegaly, bone growth due to increased production of growth hormone by the anterior pituitary gland progressed by endochondral ossification of articular cartilage, periosteal apposition of bone and moulding resorption of bone. Widening of the lower dorsal vertebral bodies was present in six of 12 acromegalic patients. Above and below this level the vertebrae tapered off to normal width. Apophysial joints were enlarged, with resulting kyphosis, in some instances with pain and signs of nerve root involvement. Costochondral junctions were sometimes enlarged. Tufting of distal phalanges, with cortical thickening, broadening and coarsening of phalanges, also occurred. Because of the nature of bone growth in acromegaly, degenerative joint changes, osteophytosis and kyphosis were frequent. 680 Two clinical types of acromegalic arthropathy were reviewed. The first was an uncommon form seen in slowly progressive cases of long standing, and was characterized by limitation of motion of joints because of massive bony overgrowth and deformities of bone ends. The second was a more common type, characterized by pains in the back and extremities, with soft tissue enlargement about joints, synovial thickening, recurrent effusions and abnormal mobility.956

An unusual case was reported of Gaucher's disease with humeral-acromial joint involvement which appeared immediately following acute rheumatic fever and 17 years following splenectomy. The "Erlenmeyer-flask" type of metaphysial expansion of the lower portion of the femur was one of the x-ray manifestations of Gaucher's disease. The bone cortex was thin and the pattern was irregular. These findings were similar to those of metaphysial dysplasia, but the nonosseous features of Gaucher's disease distinguished it. 1020

Osteitis Pubis. An inflammatory lesion involving the structures of the anterior pelvic girdle might complicate retropubic surgery. Treatment had been generally unsuccessful until the recent application of corticotropin and cortisone. Two cases with "dramatic improvement" were reported.⁷⁵⁶

CONGENITAL DEFECTS INVOLVING JOINTS

Ehlers-Danlos Syndrome. Arthrochalasis or exaggerated laxity and mobility of the joints, along with hyperelasticity of the skin, fragility of the skin and blood vessels and, less commonly, molluscoid pseudotumors over bony prominences and subcutaneous nodules, were again listed as the cardinal features of the Ehlers-Danlos syndrome. The genealogic tree of a 20 year old soldier with all of the stigmata of this syndrome showed nine of 28 relatives with the same disorder. Variable combinations of the features of this condition resulted in incomplete syndromes, or "formes frustes," and overlapping of these manifestations with those of other heritable connective tissue disorders at times produced complex clinical results. Coexistence with osteogenesis imperfecta, with ectopic bone formation, os and with Cushing's syndrome and occlusive arterial disease 1189 was reported. Additional case histories were described. So,

Morquio-Brailsford Syndrome. Lack of agreement on criteria for diagnosing classic osteochondrodystrophy (Morquio's disease) was apparent in a review of the literature by Lipschutz. Among the cardinal manifestations were a normal head, a short neck and trunk, kyphosis, pigeon-breast and multiple deformities of the extremities, with knock-knees, flat feet, and knobby swellings at the knees and elbows and at different levels of the spine. The most important

single x-ray finding was that of universal vertebra plana (flattened and wedge-shaped vertebral bodies with irregular edges). In the long bones the most constant and diagnostic finding was defective and irregular calcification of the proximal ends of the femurs, with bending of the femoral necks and flattening of the proximal ossification centers, with enlarged acetabular cavities. Transmission as a mendelian recessive trait was implied in a report of seven cases of typical Morquio-Brailsford syndrome in males and females of three Sudanese families of consanguineous parentage. [This report brought the total in the world literature up to 78 cases.—Ed.] Other case reports recognized the existence of atypical "formes frustes" and overlapping with other developmental skeletal dystrophies. [1270, 1408]

The hereditary condition known as dysplasia epiphysialis multiplex was distinguished from osteochondrodystrophy by Fairbank in 1947 by the characteristic anterior tongue-like prolongation of the vertebral bodies, the angular kyphosis, and the more severe involvement of the epiphyses, particularly of the acetabulum. Fourteen cases of the former condition were reported in three families. 1880

Arthrogryposis Multiplex Congenita. The first reported occurrence in identical twins supported the theory of hereditary transmission of this rare disorder. Six of 54 patients had ancestors with similar joint deformities. The possibility of different modes of pathogenesis in different patients was proposed. Possibly related to this condition was a bilateral congenital flexionadduction deformity of the thumbs observed in five infants. 2179

Gargoylism. Clinical and radiologic features were reviewed. ¹⁰²¹ Formerly thought to be a lipid, the abnormal "storage material" in this disorder was believed to be a mucoprotein, ¹⁵³² a mucopolysaccharide, ¹⁴¹¹ or a mixture of a polysaccharide and a glycolipid. ²¹²⁸ Different routes of hereditary transmission were proposed. A sex-linked recessive gene was implicated in a genetic study of an English family with 12 gargoyles in three generations. ⁴⁶⁶ Cor pulmonale due to gross thoracic deformity was reported in two brothers with gargoylism. ⁶⁸¹ Familial dysplasias of long bone epiphyses and diaphyses were discussed at length. ^{1020, 1021} Congenital coxa vara, arthrokatadysis and developmental dysplasia of the hip predisposed to degenerative joint disease in later life. ^{1030, 2270}

Pseudo-Pseudohypoparathyroidism. In 1952 a syndrome with all of the usual anatomic stigmata of pseudohypoparathyroidism, with normal serum calcium and phosphorus levels, and without clinical evidence of inability to utilize Parathormone, was described by Albright and associates. They called this new syndrome "pseudo-pseudohypoparathyroidism." Two additional cases of this dyschondroplasia syndrome were reported, with deformities of the joints due to anomalies of the metacarpals, metatarsals and phalanges attributed to a genetic defect independent of any hypoparathyroid deficiency. 1451, 1787

STRUCTURE AND FUNCTION OF ARTICULAR TISSUES

Basic Structure of Connective Tissue

Great interest in connective tissue and its characteristics continued to be manifested. The recent studies emphasized the statements of Theophile Borden in 1797, quoted by Klemperer, 1188 that it was "the cellular organ" and "the most extensive and useful of all the parts of the body," and "the seat of numerous

diseases and the site of many manifestations of animal life." The gradually changing theories and increasing knowledge of the development, nature and significance of connective tissue, as well as the alterations in disease, were the subject of many reviews, 844, 1412, 1577, 1926 especially complete being those by Krompecher 1166 and Klemperer. 1153 The tendency to draw too far-reaching conclusions from the as yet inadequate knowledge was emphasized. 1166 The heritable disorders of connective tissues were succinctly reviewed by McKusick. 1411 The elements of connective tissue were shown to have their own innervation, with terminations on cells and on collagen fibers. 4, 1148 [Other recent advances of great interest concern studies with carrageenin, 2227 plastic sponges for obtaining isolated samples of connective tissue, 239 and metabolism of carbohydrate components of connective tissue. 310—Ed.]

The available knowledge of the effect of mucopolysaccharides on fibrillogenesis and of the binding between mucopolysaccharides and proteins in connective tissue was reviewed. On the basis of swelling experiments (using sclera, cornea, tracheal cartilage and a model system of pigskin gelatin and K-chondroitin sulfate), Loeven 1287 concluded that both the natural and the model systems were "complex systems" in the sense defined by Bungenberg de Jong, and assumed that in vivo the complex was formed by mucopolysaccharide molecules, the collagen molecules situated at the periphery of the collagen fibrils and the collagen network between the fibrils. 1289

In the connective tissue formation, alkaline phosphatase was found in association with recently formed collagen. However, it was found only in areas in which there was other proliferating tissue, such as epithelium. Collagen fibers formed where fibroblasts were, and when traction was constant, but could also form in a cell-free solution. Survival and multiplication of connective tissue cells in explants of heart muscle from five day old rats were found to be dependent upon substances containing sulfhydryl on disulfide groups.

Collagen and Other Fibrous Components. Collagen. The problem of the formation, structural organization and precipitation of collagen was the basis for reviews by Randall 1695 and Bear. 125 Further study by electron-microscopy confirmed an increasing width of the human collagen fibril in skin during fetal life, but not subsequently.93, 1101 However, increased diameter of collagen fibers with increasing age was noted in bone: 150 to 530 Å in infants, in contrast to 1,000 to 1,500 Å in the 80 year old group. 1751 A high proportion of narrow fibrils and tapered ends was found in granulation tissue.98 The similarity of size of collagen fibrils in sections of skin and in teased preparations was confirmed.1271 Collagen fibrils in alopecia totalis showed no alteration.2238 Marked decrease in the changes produced by collagenase was found with increasing age. 1098, 1099 In extracted human skin collagen, three types of breakdown structure were found, each ultimately disintegrating to a "bead," thought by Keech 1100 to be the smallest collagen macromolecule now possible to photograph. Electronmicroscopic studies of collagen fibrils cut transversely and longitudinally indicated that collagen fibrils have a tubular structure. 1181 [More evidence is necessary for confirmation.-Ed.] Addition of anticollagen serum to cultures of dermis of chick embryos was detrimental to fibrogenesis, and resulted in formation of intercellular amorphous material and disappearance of the cytoplasmic granules seen in fibroblasts grown in normal serum. 1742 [Evidence for conclusions as to the nature of the cytoplasmic granules is lacking.—Ed.]

From studies of the formation of the various structural forms of collagen from an acid solution and their interconversion, the unit of collagen structure was considered 843 to be a thin particle varying in length from 1,500 to 3,000 Å, called tropocollagen. Light scattering, osmotic pressure, sedimentation constant, intrinsic viscosity and flow birefringence studies also indicated a rigid, rod-shaped particle with a diameter of 14 Å and a length of 2,900 Å.²⁰³

Electron-microscopic study of thin sections of connective and skeletal tissues of fowl embryos demonstrated submicroscopic filaments in osteoblasts, osteocytes, chondroblasts and fibroblasts. The findings suggested that the intracytoplasmic filaments were concerned with fibrogenesis, but only tentative hypotheses as to their relation-

ship to extracellular collagen fibers could be made. 1017, 1018

Attempts to describe an exact molecular configuration which was in agreement with the x-ray diffraction, infra-red absorption, electron micrograph and chemical data continued. 1684, 1685, 1687, 1685, 1685, 1689, 1729 It was concluded that the facts were best explained by a helical structure of three polypeptide chains, each of which had 10 residues in three turns of a lefthanded helix, and the three chains were further wound into a superhelix. 1689 The proposed two structures 1729 and the backbone structure 441 were also similar. The high negative optical rotation of collagen (-350°) was interpreted as being related to the helical configuration. 403 Smallangle x-ray diffraction patterns suggested that, although the long-spacing of collagen might vary, there was a constant unit of 32.8 Å. 2258

The effect on shrinkage temperature of various specific reagents indicated that four fifths of the stabilizing bonds in rat-tail tendon were probably hydrogen bonds, ¹⁰¹⁵ and suggested that linkages between collagen and chondroitin sulfate accounted for one fourth of the stabilizing bonds. On the basis of acetylation of bovine collagen, which blocked three out of four hydroxyproline groups and reduced the shrinkage temperature to that of cold water fishes, it was suggested ⁸⁵³ that the hydroxy group resisting acetylation formed the bond (probably – O.CO –) mainly responsible for the stabilization of telost collagen. Paper chromatography of dinitrophenyl derivatives of soluble collagen showed very small amounts of DNP-aspartic and DNP-alanine. About one third of the α-amino groups were not available to react with dinitrofluorobenzene.

When collagen fibers were dried after being kept in sodium hydroxide, x-ray diffraction showed various salts crystallized in the collagen. 1086 Further evidence was obtained that hydrolysis of the amide groups, and not removal of an amino-sugar component, was responsible for the lowering of the iso-electric point of collagen under the action of alkali. 2188 The similarity of titration curves of collagen and "pigskin gelatin" (produced by acid treatment of collagen) suggested that the latter is collagen rendered soluble, and that its iso-electric point of pH 9.25 must be that of collagen. 2188 Very few changes in amino-acid composition were noted on conversion of collagen to gelatin, and collagens and gelatins from several mammalian sources were closely similar. 580 The hydroxyproline and the hexosamine content of a gelatin fraction from rat skin increased with age in both sexes. 1598 The specificity of bacterial collagenases for collagen and gelatin was emphasized. 1329

Further study of the periodic acid Schiff staining of collagen suggested that cleavage of the nonglucosamine polysaccharide complex in the fibers explained the reaction.

This hypothesis needs further supporting evidence.—Ed.] Differences between normal collagen and that showing "basophilic degeneration" were described by histochemical and microspectrophotometric methods.

Interpretation of staining

reactions remains hypothetic.—Ed.]

Valuable reviews of the nature of the soluble collagen components and their possible role as precursors have appeared. 892, 1188 A gradual decrease in the amount of citrate-soluble collagen removed with each extraction suggested 240 that a specific

soluble fraction was being removed. Other observers, 892 however, concluded that there was not adequate evidence that the change from citrate-soluble to insoluble collagen was discontinuous. On the basis of studies using C14 glycine, it was concluded that the alkaline-soluble collagen was a precursor of other collagens, but that the citrate-soluble collagen was a precursor of other collagens; the citrate-soluble fraction was not necessarily an intermediate. From the physicochemical properties of the citrate-soluble fraction ("procollagen"), it was suggested that the relation of procollagen to fibrillar collagen may be that of monomer to polymer, with the added participation of other substances, such as glycoprotein and mucopolysaccharide, 1373b The amino acid composition of citrate-soluble collagen was essentially the same as that of hide collagen. Only small amounts of hexosamine, glucose, galactose and mannose were found in hide collagen or in citrate-soluble collagen.^{240, 1480} The problems encountered in using various sugar methods for protein hydrolysates were discussed.1489 The dispersion of collagen fibers to separate fibrils by acid buffers suggested that the soluble collagen lies in the fibers between fibrils.2075 Feeding experiments in young rats, using C14-labeled L-lysine, indicated that the hydroxylysine of collagen is formed from lysine. 1918 Radioactive acetate utilization indicated that the proline of rabbit skin collagen is synthesized in situ.1183

Reticulin. Study of the relationship of reticulin and collagen furnished further evidence of the similarity. No differences could be detected by electronmicroscopy. 1005 The argyrophilia of reticulin was shown to be dependent upon the complex of the ground substance and fibers. 1005 Reticulin was found 580 to be similar to collagen in amino acid composition, but to have a much lower hydroxyproline content. 556 Both collagen and reticulin were readily hydrolyzed by collagenase, but only slightly digested by trypsin. 550

Elastin. The problem of the nature of elastin and the relationship to collagen was well reviewed.872 There was widespread agreement that collagen fibrils are always closely associated with elastic tissue, but difference of opinion as to whether collagen can be transformed into elastin. From electron-microscopic study of collagen treated with alkalies or trypsin, it was concluded by some that collagen could be transformed into elastin. 308, 872 On the basis of histologic studies of the abnormal "elastic" fibers that accumulate in various disease states, it was concluded that the so-called elastotically degenerated fibers might represent an alteration in collagen or reticulin fibers. 780 However, the susceptibility of abnormal "elastic" fibers to elastase was considered to be evidence that they represented alterations in elastic tissues and not in collagen. 677 Collagen of ligamentum nuchae that remained after removal of elastin by elastase was extensible.2248 Mucopolysaccharides were apparently very important in determining tensile properties of elastic tissue, but not of the elastin after removal of collagen.²²⁴⁸ [The caution expressed by the authors in interpreting the results in terms of molecular structure is well justified.—Ed.] Metabolic turnover in elastin in the adult rat aorta, as determined after intraperitoneal injections of α-C¹⁴ glycine, was very slow, in common with the major portion of collagen. 1924 [The variety and opposing nature of interpretations indicate the need for further study of the problem; the nature of elastin remains ill defined.-Ed.]

No specific cell has been shown to have elastoblastic activity, 303 but elastic material was never produced in the absence of cells. 854

The electron-microscopic study of elastic tissue disclosed fibers, thick and parallel in ligamentum nuchae but branching to form sheetlike structures in the aortic wall, associated with an amorphous cement material. 878, 874 Two peaks in the pH activity curves suggested the presence of two enzymes in elastase which acted on the two components of elastin. 875 Pancreatic elastase and a bacterial chondrosulfatase both caused disappearance of metachromatic staining with toluidine blue in aortic wall sections and subsequent lysis of elastic lamellae. 1606 [Interpretation of staining reactions must be made with caution.—Ed.]

The soluble protein derived by mild hydrolysis of elastin was composed of two fractions (a and B) of similar amino acid composition but markedly different physical properties, 1852, 1853 Determination of N-terminal residues suggested that \(\alpha\)-protein has 17 polypeptide chains (containing 35 residues), and \(\beta\)-protein two chains (of 27 residues). 1858 Titration curves showed about 26 and 31 moles of α-amino residues in 105 gm. of protein in α- and β-proteins, respectively. 140

Fibrin. Preliminary observations suggested the possible value of difference in susceptibility of fibrinolytic enzymes in studying fibrinoid substances. 2180

necessary in interpreting such differences.-Ed.]

Ground Substance. The components of the "ground substance" of connective tissue continued to be the subject of investigation. 636, 2154 An excellent critical review of the mucopolysaccharides was presented, including the components, the biosynthesis by streptococci, and the metabolism in connective tissue.548 The available knowledge on the carbohydrate components of connective tissue, and the scanty information on alterations with disease, were reviewed. 319 The evidence that the protein component is derived by direct transudation from the blood was reviewed. 1158

Mucopolysaccharides and Mucoproteins. Isolation and characterization of mucopolysaccharides from various tissues have continued. In bovine heart valves, hyaluronic acid in addition to chondroitin sulfates B and C was characterized. 496 Analysis of human nucleus pulposus showed both chondroitin sulfuric acid and keratosulfuric acid. 742 An acid mucopolysaccharide isolated from human leukocytes and urine was identical by chromatography with chondroitin sulfate; 1182, 1183 the 24-hour urine excretions were greater in males than in females. An acid mucopolysaccharide low in sulfate isolated from bovine cornea was characterized as chondroitin, thought to be the precursor of chondroitin sulfate. 483 A polysaccharide containing uronic acid hexosamine and one or more sugars was found in human euglobulin, and was increased in plasma from 10 patients with rheumatoid arthritis.78 Substances containing carbohydrates and presumably proteins but no glucuronic acid were isolated from connective tissues of cattle. 793 In extracts of rats' limbs, at least three polysaccharides were observed and, in costal cartilage, at least two. 1925 Histochemical studies in gargoylism indicated that the material infiltrating tissues other than neurones contained polysaccharide as well as a phosphatide. 490 [Further evidence is necessary to support the suggestion that the primary disturbance is one of mucopolysaccharide metabolism.

Advances in methods for the study of mucopolysaccharides were reported. Separation, identification and determination of glucosamine and galactosamine by paper chromatography were made possible by transformation of the amino sugars.2017 Hyaluronic acid and chondroitin sulfuric acid were separated by column chromatography using lauryl amine,149 and by slab electrophoresis.1831 A method for quantitative estimation of hyaluronic acid in human intervertebral discs was described. 1898 Methods for determination of chondroitin sulfate and hyaluronate in the absence of protein were based on binding of ferric ions. The micromethod was used to assay hyaluronidase. 515 The relative distribution of polysaccharide in the various serum protein fractions of normal men (ranging from 13.1% in albumin to 27.8% in a globulin) was determined by the Grönwall and Köiw method of staining protein-bound polysaccharide in paper electrophoresis strips.187 Correction for the error caused by tryptophan in the method of Graff for determination of protein-bound

hexose in normal blood serum gave higher values.187

The marked variations in the staining of mucopolysaccharides in animal tissues with many methods and the resulting dangers of interpretation were emphasized by Gomori.812 The difficulties of interpretation of metachromasia, the periodic acid Schiff method, the "pH signature" and enzymatic removal of stainable material were further emphasized, 141 but a slow advance in histochemistry was pointed out.

The findings in connective tissue obtained by subcutaneous implantation of a polyvinyl sponge were summarized.²⁸⁸ A "loosening" of the bands of collagen, an increase in mast cells and decrease in concentration of protein and cholesterol were observed after relaxin administration.

In rats given total body irradiation, Evans blue spread much more rapidly and widely, after five days, than in controls.²¹²¹ In rabbits, India ink subcutaneously caused inflammation which made it unsuitable as an indicator when substances with anti-inflammatory effects were tested.⁶⁰² Decreased dermal permeability following burns was counteracted by dibenamine, and was considered to be due to vasoconstriction.⁶⁰² Antihistamines had no consistent effect on dermal spread.⁶⁰³

The concentration of hexosamine in orbital connective tissues decreased with age in normal and in hypophysectomized rats, but not in thyroidectomized animals. Growth hormone produced an increased amount of connective tissue but no change in concentration of hexosamine.²⁰¹ In the skin of rats, "ground substance" was more abundant in males than in females, with a higher hexosamine concentration in adolescence than in maturity.¹⁵⁹⁸

Mast Cells. The confusing and controversial reports on the nature and function of mast cells were reviewed, and the overinterpretation of morphologic findings in terms of the secretory function of mast cells was emphasized. Histologic studies demonstrated that all alterations previously ascribed to physiologic change or various drugs were equally common in normal controls. 509 Morphologic alterations produced in mast cells by colchicine, nitrogen mustard and x-rays were described. 1103, 1104 In vivo staining with toluidine blue in hamsters' cheek pouches demonstrated many granules in the mast cells and some extracellular granules.2182 The reported evidence for heparin and histamine in mast cells was reviewed. 1788 The impossibility of concluding that the mast cells were the source of the increased stainable polysaccharide in tissues of irradiated rats was pointed out.2121 [There is much recent evidence to suggest that the mast cells may play a major role in the pathophysiology of the connective tissue diseases. Established as a source of histamine, heparin and probable producers of serotonin and hyaluronic acid, these pluripotential cells have been described by Asboe-Hansen as the target cell for the transmission of hormonal influences at the tissue level. The reasons pointing toward these cells as possible links in the connective tissue diseases have recently been summarized.1949—Ed.]

Amyloid. In mice treated with sodium caseinate injections, nitrogen mustard caused a marked increase in amyloid deposition, and in a patient with Hodgkin's disease, amyloidosis followed treatment with nitrogen mustard and roentgen irradiation. Amyloidosis was induced in mice by injection of the Freund-type adjuvant but not by the bacteria, oil or emulsifying agent alone. Electrophoretic and chemical analysis of tissue from two cases of amyloidosis showed elevation of a1-globulin and associated mucopolysaccharide in one, and of a2- and β -globulins with corresponding mucopolysaccharides in the other. The suggested hypothesis—that amyloid represented tissue localization of an abnormal blood protein complex—was similar to that reviewed by Klemperer. A substance staining like amyloid but susceptible to the action of elastase was found in many malignant tumors. Plant in many malignant tumors. In the chemical composition of a relatively pure amyloid deposit obtained from the liver of a patient dying of tuberculosis showed 2% neutral sugars (glucose and glucosamine), 1.5% hexosamine and 0.6% uronic acid.

Hyaluronic Acid. From light scattering measurements, it was concluded ¹⁹⁸ that hyaluronic acid particles are highly swollen spheres (with diameter, 210 mu, and molecular weight, 8.0 by 10⁶), while from another, similar study ¹²²⁰ the conclusion was reached that hyaluronic acid is a somewhat rigid coil (with molecular weight

2.8 by 4.3 by 10⁶). The intrinsic viscosity at pH 7.0 was 33.6.¹²²⁰ The diffusion coefficient of hyaluronic acid was 1.0 by 10⁻⁷ cm² sec⁻¹, and the molecular weight calculated from the sedimentation coefficient (3.0 S) and the partial specific volume (0.86) was 5.2 by 10⁵.¹⁰⁴³ The infrared absorption spectra of hyaluronic acid from umbilical cord, Rous's chicken sarcoma and a human myxoma were almost identical.¹⁵⁶⁵ The reciprocal of the sedimentation constant of hyaluronic acid in synovial fluids corrected for the effect of the albumin had an almost straight-line relationship to the log of the Ostwald viscosity.¹⁰⁵⁸ Oriented fibers showing considerable birefringence were prepared by evaporating solutions of sodium hyaluronate in a wedge between a glass slide and cover-slip.²⁰⁵³ The marked effect of sodium chloride on flow birefringence, viscosity, sedimentation and light scattering of hyaluronic acid was demonstrated.¹⁰⁷

The ability of human synovial tissue cultures to produce substances forming characteristic mucin clots was confirmed.⁸⁴⁶ In cultures of rat subcutaneous tissue and of embryonic bone, skin, tendon, epiphysis, aorta and pericardium, mucin clots could be formed and could be inhibited by hyaluronidase.⁸⁴⁶ Synthesis of hexosamine in cultures of rabbit subcutaneous and synovial tissue was demonstrated.²²⁰ [The production of mucopolysaccharides by synovial cells in a simplified tissue culture medium has

recently been reported.848-Ed.]

Further studies of the biosynthesis of hyaluronic acid by Group A hemolytic streptococci, utilizing C¹⁴N¹⁵ glucosamine, demonstrated that glucosamine was incorporated without previous deamination. It could not be concluded that N-acetyl-glucosamine was an intermediate.⁵⁴² Hyaluronic acid was produced by 47 strains of 29 types of Group A hemolytic streptococci, and in six more strains after passage through mice, and in two after growth in media with penicillin.⁶⁵⁰, ⁶⁵¹ The increase in hyaluronic acid in cultures of hemolytic streptococci, type 24, by penicillin was presumably due partly to inhibition of release of hyaluronidase from the cells and partly to a decreased production of enzyme, and possibly to increased production of hyaluronic acid.¹¹¹³ [Interpretation of the cause is difficult in such a system.—Ed.] In a resistant strain, penicillin caused loss of most of the ability to produce hyaluronic acid.¹¹³

Hyaluronidase. In reviewing the available knowledge on hyaluronidase, Dorfman 548 indicated that the physiologic and pathologic role of these enzymes was not yet clear. Evidence that more than one enzyme was necessary to cause breakdown of hyaluronic acid to monosaccharides was presented. Hyaluronidase was produced by 65 of 78 strains from all types of Group A streptococci except 9 and 28. Some strains produced both hyaluronidase and hyaluronic acid. Penicillin caused an increased production of hyaluronidase in a sensitive strain. In a carbonic acid-bicarbonate buffer, serum increased hyaluronidase activity, and this effect was

augmented by magnesium and decreased by calcium.2008

Hyaluronidase injected between the dermis and panniculus in rats produced inflammation varying with the dose.²²⁸⁰ Both hyaluronidase and hyaluronic acid in certain dilutions caused formation of subdermal tumors.²²³⁰ Streptococcal hyaluronic acid, if partially depolymerized by testicular hyaluronidase, caused a significant spread in rabbits and guinea pigs.¹⁸⁵⁹ Hyaluronidase or partially depolymerized hyaluronic acid enhanced the absorption of atropine injected subcutaneously.⁸¹ The adrenal-stimulating action of corticotrophin was enhanced by simultaneous injection of chlorphyllin.⁴⁰⁴ [There is no evidence to support the suggestion that the effect is due to antihyaluronidase activity.—Ed.] Pneumococcal hyaluronidase which did not attack chondroitin sulfate hydrolyzed chondroitin at the same rate as did hyaluronate.⁴⁶⁸

Other Mucopolysaccharides. Chondroitin sulfuric acid isolated from rabbit skin by slab electrophoresis differed from that of cartilage, and raised the possibility that two sulfated polysaccharides were present in skin. By infrared spectroscopy, two isomers of chondroitin sulfuric acid were characterized, both found in bovine articular

cartilage and trachea but only one in nucleus pulposus, 1565 The marked differences between chondroitin sulfate B and both A and C were emphasized. 1437

Knowledge of the metabolism of the sulfomucopolysaccharides obtained by studies of sulfate exchange by isotope technic was reviewed in considerable detail. 231 Further work indicated that the "liver factor," which stimulates sulfate exchange in cartilage slices, was found also in brain, muscles, lung and serum, and was apparently glutamine.232, 233 Sodium salicylate and, to a lesser extent, acetylsalicylic acid and benzoic

acid, inhibited sulfate exchange in cartilage slices.280

After intraperitoneal injection of S35 labeled sodium sulfate into rats, the highest concentration was found in the zone of cell columns of epiphysial cartilage, and a high concentration in dense fibrous tissues. The radioactive materials were still in cartilages at six days in one study, 484 but for 38 days in another. 576 Granulation tissue in guinea pigs fixed Sas sulfate, after the seventh day, chiefly in a sulfurcontaining mucopolysaccharide, but the evidence was inadequate to prove whether it was chondroitin sulfuric acid. The uptake was less in scorbutic animals. In vitro, the uptake was inhibited by disruption of cells as well as by many enzyme inhibitors. 1188

Close correlation was found in chick embryos and in mice between autoradiographic localization of S85 and various staining methods for mucopolysaccharides.38, 467 The localization of S²⁵ in silicotic foci to regions where fibroblasts were concentrated was considered as further suggestion that fibroblasts form mucopolysaccharides. 468 The half-life times of hyaluronic acid and the chondroitin sulfuric acid fraction from rabbit skin determined with use of C14 carboxy-labeled acetate were 1.9 and seven days, respectively, apparently representing the rate of synthesis of the N-acetyl portions of the polysaccharides. The turnover rate of polysaccharide sulfate in costal cartilage in rats injected with Na, S35O4 was 17 days. 1925 After intravenous injection in guinea pigs of labeled polysaccharide fractions of Klebsiella pneumoniae, the adrenal was the site of the greatest concentration of C14, and it persisted for two months. 1063

Neither auto-antibodies nor arthritis was produced by injection into rabbits of a vaccine containing rabbit chondroitin sulfate and hemolytic streptococci. 199 [The contrast with the results of the series quoted by them, in which human chondroitin sulfate was used, indicates the need for further investigation.-Ed.] In alloxan-diabetic rats whose diabetes was aggravated by ACTH administration, the serum polysaccharide level rose markedly.2098 The insecticide DDT produced degenerative changes in the fascicular zone of the adrenal cortex in rabbits, and lowered the serum poly-

saccharide and glucose levels.2009

Synovial Tissues and Synovial Fluid

Anatomy. An excellent, concise review of the anatomy and physiology of the blood and nerve supply of joints was presented, with emphasis on the many unsolved problems.744 Differentiation of blood vessels in synovial villi and folds occurred in the second half of uterine life in dogs and cats, and was completed after birth. 959 In joints of dogs and cats, by injection of India ink into the aorta, the vascularization of the synovial tissues could be differentiated into four layers: (1) vascular plexus, (2) capillary network, (3) the basal arteries and veins, and (4) the large articular vessels.959

Joint Fluid. Extensive viscosity studies have sought further means of determining the degree of abnormality of hyaluronic acid in joint fluid. 695, 1057, 1059, 2089 The degree of anomalous viscosity correlated with viscosity at constant stress, and furnished a sensitive test of the degree of degradation of hyaluronic acid. 190, 1059, 2089 Thin fluids, in contrast, were shown to be almost true fluids. 190 Specific viscosities showed marked differences between fluids in osteoarthritis

and those in rheumatoid arthritis, but limiting and anomalous viscosities indicated no difference in degree of polymerization of hyaluronic acid in the two groups.

Viscosity and sedimentation measurements suggested interspecies differences in specific properties of hyaluronic acid.

[Consideration of traumatic fluids from humans as comparable for determination of species differences in particle weight with normal fluids from sheep and ox is not justifiable.—Ed.]

The hyaluronic acid protein complex prepared by the method of Ogston and Stanier contained proteins similar to serum proteins electrophoretically and immunologically, and by sedimentation. At pH 5.8 α -globulins predominated, α - and

β-globulins at pH 7-8 and α-globulin at pH 10.470, 1552

Cholinesterase activity was demonstrated in synovial fluid by the Michel electrometric method, and no consistent difference was observed between fluids from rheumatoid arthritis and from trauma. The aminotripeptidase content varied greatly in synovial fluids from different diseases, the lowest being in degenerative joint disease and the highest in rheumatoid arthritis. Pelucuronidase was demonstrated chiefly in leukocytes, but also in cell-free fluid. In degenerative joint disease the concentration was low, but was markedly elevated in psychogenic rheumatism and severe rheumatoid arthritis. 1027

The sodium and potassium concentrations in normal synovial fluid from humans, obtained during life and post mortem, were essentially the same as those reported for normal cattle fluid.²²⁶⁸

The albumin concentration in synovial fluid determined by sodium sulfate precipitation was lower than that by electrophoresis, and the pseudoglobulin considerably exceeded the sum of α_1 and α_2 fractions. The total albumin and globulin concentration was low (0.4 gm. per 100 c.c.) in normal joints, but increased after trauma. Mucin concentration was highest in the joints with old cartilage injuries. Acutephase protein was found in fluids from rheumatoid arthritis and spondylitis, but not in osteoarthritis or traumatic arthritis. The many specific properties of traumatic arthritis.

Methods for determining concentration of hydrocortisone in synovial fluids were reported. A28, A75 In rheumatoid arthritis the concentration was the same in synovial fluid as in blood. No significant increase occurred with oral cortisone therapy. A30 Clinical improvement was observed in nine patients in whom the fluid concentration decreased within 30 minutes after intra-articular injection, but not in the one in whom the decrease occurred after two hours. Intra-articular injection of hydrocortisone in rheumatoid arthritis caused an increase in degree of polymerization of hydrocortisonic acid, and usually an increase also in concentration. Intra-articular injection of hydrocortisonic acid, and usually an increase also in concentration. Intra-articular injection of hydrocortic acid, and usually an increase also in concentration. Intra-articular injection of hydrocortic in the decrease in hydrocortic inhibitor activity also reported is less impressive, and the suggestion that the hormone acted by influencing synthesis of hydrocortic acid needs further corroboration.—Ed.] Hydrocortisone also caused a lowering of the high sodium and potassium levels in effusions in rheumatoid arthritis, and acute-phase protein disappeared temporarily.

Physiology of Synovial Tissues. Following intra-articular injection of Diodrast in normal rats' knees, 0.09 c.c. entered the joint and thus suggested the approximate size of the cavity. The average removal time after a one-minute injection was 30 minutes, and the cumulative outflow during continuous intra-articular injection was 0.064 c.c. in 14 minutes. Thorotrast, in contrast, was still visible in the joint after three days. 1406 The importance of technical details in evaluating removal of substances from joints was emphasized. An increased rate of removal of phenolsulfonphthalein with hyaluronidase was again noted by Moffett, using Diodrast. 1406 Results with cortisone varied from reduced permeability 1800 to no alteration, 1406 and with desoxycorticosterone acetate,

from increased removal 604, 1860 to no alteration. 1466 Similarly, adrenalectomy caused no change in removal of phenolsulfonphthalein in rabbits as tested by Baeder and Seifter, 80 but increased removal of Diodrast in rats studied by Moffett. 1467 Preliminary treatment of rabbits with alloxan decreased the resistance to fluid flow through synovial membrane, with disappearance of the "breaking-point." 605 Compounds related to benzoyl carbinol and also phenylbutazone decreased removal of phenol red from rabbits' joints. 165 [Conclusions as to the effect of various substances or the mechanism of action must await further studies. In many cases, the nonspecific effect on permeability of the irritating action of the injected material on the synovial tissues cannot be estimated.—Ed.] Greatest absorption, as indicated by staining after intra-articular injection of azocarmine-C, occurred in the villi and folds of the areolar and adipose areas of the synovial tissues. 1650

Following oral or intramuscular administration procaine penicillin G, streptomycin, Aureomycin, Terramycin and chloramphenicol were found in small amounts and in only a small percentage of joint effusions, in contrast to potassium penicillin G, which was found in all of the five joints tested. 1046 [The lack of blood levels makes interpretation difficult. The conclusion that antibiotics, other than potassium penicillin G, are not of value in management of pyogenic arthritis is unjustified.—Ed.] In joints of normal dogs, penicillin reached one fifth to one-half, and streptomycin one tenth to one fifth, of the blood level. 1058

Demonstration of the fact that all but insignificant potentials in synovial tissues could be eliminated by substituting plastic needles for those of stainless steel made it questionable whether the potentials were related directly to metabolic activity of the tissues. 1709 In synovial tissues from rheumatoid arthritis, the villi had a higher oxygen consumption and glucose utilization than did the membrane itself. Hydrocortisone in vitro inhibited the oxygen uptake and glucose utilization. 2083 Periarticular injection of procaine caused a rise in intra-articular temperature. 692

Physiology of Other Joint Tissues. A comprehensive review appeared of the altered physiology in joints as observed in various forms of chronic deforming arthritis. ¹⁸⁶⁸ Included in this report were studies of synovial fluid, joint and muscle potentials, temperature and circulation.

Joint and Muscle Pain. Two types of sensory units were demonstrated histologically ²⁴² in the fibrous capsule of the cat's knee joint: the spray type, responsible for slowly adapting discharges from the posterior articular nerve during joint motion; and the less common lamellated type, responsible for rapidly adapting discharges. A study based on recording of discharges only, however, suggested that there was only one type of proprioceptor. ⁴⁰⁸

The pain in chronic rheumatic disease was considered to be muscular and due to ischemia, ⁵⁵⁷ but the so-called "ischemic pain" could be produced in muscles with a free blood supply and was considered to be due to pressure on nerves. ^{1122, 1128} [Further direct evidence will be necessary to clarify this problem. —Ed.] Referred pain in the knee was considered to be due to fascial abnormalities in the midlumbar and midsacral regions. ⁵²² [The nature and effect of the abnormalities are not clear—Ed.]

Joint Motion. Methods of measuring muscle and joint function were reviewed. 1811 A strain-gauge dynamometer for measuring muscle strength was considered to be suitable for research and clinical use, supplementing a muscle charting system in the latter case. The simple protractor type of arthrometer

was thought to be most generally useful in measuring range of joint movement. The importance of standardization of details and of nomenclature was emphasized. A simple method of recording joint motion, essentially that described by Cave and Roberts, was elaborated and illustrated in detail. Comparative anatomy, apparently without histologic control, was used to elucidate the role of intra-articular fibrocartilage. Study of 60 vertebrate joints demonstrated that joints containing fibrocartilage were capable of two types of motion: ball and socket, such as flexion and extension, and plane joint motion, a to-and-fro gliding without angular displacement. On the containing fibrocartilage were capable of two types of motion:

Physiology of Cartilage. The exact physiochemical state of the constituents of cartilage and the nature of their interrelationships were discussed but remained poorly understood. By mild extraction methods a mucoprotein was isolated from bovine cartilage, containing 30% protein, 60% chondroitin sulfate and 10% water; the protein contained no hydroxyproline. Salt precipitation and ultrafiltration studies showed the molecule to behave as a complex believed to be actually present in the cartilage. It included at least one third of the whole cartilaginous chondroitin sulfate, while most of the remaining mucopolysaccharide was thought to be bound to the insoluble matrix, possibly to collagen. The polysaccharide composition of whole cartilage was shown to change with age. In humans the uronic acid content was high in fetal cartilage, dropped sharply in early life, and then gradually diminished through old age. The hexosamine level fell more gradually. 1888

The circulatory nutrition of cartilage again drew attention. Rabbit knee cartilages were studied radioautographically one to three hours after administration of P³² or AU¹⁹⁸, the former considered to circulate as a free ion, the latter linked to serum albumin. With either isotope, darkening of the film was found in two bands, a lighter one at the joint surface of knee cartilage and a darker one on the basal surface, with a less black intermediate zone between. There were a more diffuse transition and a higher average density in exercised joints. The findings were interpreted as confirming the hypothesis that articular cartilage was nourished from both the synovial and the epiphysial surfaces, and that the rate was increased by exercise.⁶¹⁶ Intravenous injection of a dye which fluoresces in ultraviolet light produced the same results, as well as rapid uptake by the annulus fibrosus and hyaline plate of the intervertebral discs of rabbits.²⁶⁸

The cytochrome oxidase system was found in embryonic chick cartilage, the latter being capable of 200 times the oxygen uptake of adult cartilage. Sulfate fixation was stimulated by glucose and inhibited by dinitrophenol and ammonium molybdate. S³⁵-labeled chondroitin sulfate was isolated from some of the reaction mixtures.²⁴¹ Radioautographs of cartilage in young mice two hours to 17 days after injection demonstrated conclusively that the label is first taken up by the chondrocytes and subsequently appears in the matrix; perichondrial cells have a lesser uptake.^{138, 1602}

A review of studies of cartilage degeneration and regeneration concluded with three case reports suggesting that new hyaline cartilage was formed from fibroblasts even in aged individuals.⁷⁷¹ Sequential histologic study after splitting of rat xiphoid process showed that granulation tissue formed, became more fibrous and then, by metaplasia, developed into fibrocartilage which was eventually converted into "imperfect hyaline cartilage." Cartilage cell mitoses were noted to be "slow, sporadic, and incomplete." ¹⁶⁹⁷ Embryonal cartilage development was traced by S³⁵ autoradiography in chick embryos. The fact that precartilaginous mesenchyme took up relatively large amounts of S³⁵ before visible differentiation occurred suggested that

"the biological differentiation precedes the morphological." 88,84 The characteristics of cartilage and the use of cartilage implants (autogenous and preserved homogenous) were reviewed in considerable detail. 1819

Autografts and homografts of cartilage in soft tissues appeared to be viable, unabsorbed and uninvaded up to 22 months postoperatively.^{20, 449} Ox cartilage implants in human plastic surgery usually began to show absorption after 18 months, but two cases with no absorption after 20 to 28 months were reported; the cartilage pieces were found to be surrounded by a glistening, smooth capsule. The authors ascribed the lack of invasion and the capsule formation to soft tissue movement about the grafts.⁷⁷³ In contrast, transarticular bone autografting was found experimentally to hold up only if rigid fixation was maintained in the healing stages.⁷⁵⁸

Various demineralizing solutions were checked for their ultimate effect on cartilage and bone-staining properties. Appropriately demineralized cartilages were shown to take up Ca⁴⁵ in vitro. The darkened areas of the resultant radioautographs, coupled with histochemical findings, suggested a relationship to the acid mucopoly-saccharides. 187

The effect of hormones on S³⁵ fixation by cartilage was studied in vivo and in vitro. Hypophysectomy of young rats sharply reduced the fixation of the isotope in costal cartilage only, and not in tibial cap or xiphoid cartilage. Administration of growth hormone to hypophysectomized rats increased the uptake of all three sites to levels above the normal.⁵⁰⁰ In a system containing S³⁵ and slices of rat xiphoid process, contradictory results showed cortisone reducing and hydrocortisone increasing uptake; these responses seemed "to be related to some property of the steroid which bears no discernible relationship to its physiological actions." ³⁷⁴

Physiology of Bone. The knowledge of bone extracellular matrix obtained from electron microscopy was summarized. 67, 1751 As in other tissues, the collagen fibrils were arranged with periodic structures in regular alignment. The organic ground substance appeared to be globular and enclosed in the meshes of a fine inorganic framework, the spaces being 200 and 250 Å in diameter. 65, 67 The difficulties in determining the relationship between collagen fibrils and calcified cement substance and the evidence available on this problem were re-The inorganic component in bone paralleled the long collagen axis and was deposited in the band regions. Robinson and Watson 1751 concluded it was likely that some of the inorganic component was inside the collagen fibers. Haversian systems in bone were interpreted, on the basis of polarizing microscopy, as a form of crystallization of collagen analogous to the formation of spherulites from artificial polymers, with the collagen fibrils winding in a helix with its axis directed radially from the central canal, 189 Newly formed lamellae of the Haversian systems had a low x-ray absorption and metachromasia, suggesting the presence of acid-polysaccharides, presumably chondroitin sulfuric acid. 634 The rate of deposition of collagen in femurs decreased slightly as the rat grew, but that of hexosamine-containing material decreased markedly.1953 Organic matrix and collagen were demonstrated histologically and by electron microscopy in Neanderthal bone.66

The inefficient mechanism for nutrition of bone was discussed by Ham.⁸⁷⁹ In cadavers, radiopaque solutions injected into cancellous bone were rapidly removed into the venous system.⁹⁰⁶

Available knowledge of the turnover of minerals in bone was reviewed, with emphasis on the rapid exchange of ions between the labile fraction of bone and the body fluids and the supplementary action of parathyroid hormone on the more stable,

compact bone. 1415 The importance of bone in regulation of the blood level of calcium and phosphorus was discussed. 484, 1415 The calculation that the bulk of the water in hydrated bone was associated with the marrow-vascular-osteocyte space was interpreted as support for the thesis that the water in matrix around bone cells was displaced during calcification. 1752

In rachitic bone sections, inhibition of calcification by toluidine blue and protamine was prevented by high concentrations of calcium chloride. Metachromasia paralleled the calcifiability under certain conditions. The similarity of results with chondroitin-sulfate-collagen complexes was interpreted as suggesting that such complexes are involved in calcification.¹⁹⁵² In tissue cultures of rat bone, the amount of Sr⁹⁰ mobilized from the bone increased with decrease in pH of the medium. This isotope was also used in a study which demonstrated that viability of bone cells was not essential in the process of inorganic salt uptake by bone.¹⁷⁰²

The nature of osteoporosis and the types of disturbances in which it occurred were reviewed. 696, 1022 [Enumeration of the conditions seems more justified than does the attempted classification of the factors involved.—Ed.] Extreme decalcification of bones was noted in two patients with an associated severe cirrhosis of the liver. 1745 Bone density computed from densitometric readings correlated well with the roent-genologic estimates in os calcis and phalanx of finger. 762 [The error introduced by overlying tissues cannot be controlled by this method.—Ed.]

Copper deficiency in swine caused marked diminution in osteoblastic activity but no interference with growth of cartilage cells with resulting areas susceptible to fractures.⁶⁹⁷ Thyroid deficiency, induced in mice by radioactive iodine, retarded growth and ossification of the epiphysial cartilage and markedly inhibited resorption of cartilage and bone.¹⁹⁰⁵

Cortisone administration in rabbits promptly caused cessation of longitudinal bone growth with narrowing of the epiphysial plate and disappearance of metaphysial trabeculae. In the rat the changes were similar, and there was not always the previously reported increase in density of metaphysial bone. 1918 Cortisone did not alter the collagen content of rat femurs, despite the marked weight loss, but the hexosamine content did decrease. 1954 [The conclusion that the results do not aid in explaining the pathogenesis of osteoporosis in Cushing's disease is justified.—Ed.]

Hormonal Influences Upon Connective Tissues

Inhibition of inflammatory reaction by cortisone and hydrocortisone was again demonstrated in inflammation of many types. By the rabbit ear chamber technic, cortisone was shown to suppress the early vasodilatation and adherence of leukocytes to the vascular endothelium resulting from thermal injury.³⁰ Cortisone suppressed the reaction to implanted cholesterol pellets, whereas desoxycorticosterone pellets, which caused less reaction than cholesterol, did not.³⁵ Hydrocortisone was more effective than cortisone in mice in reducing allergic inflammation and that induced by histamine or pyrogen.⁵⁵¹ In granuloma pouches in rats, hydrocortisone applied locally and estradiol-benzoate lessened the inflammatory reaction, whereas compound S and desoxycorticosterone acetate increased it.^{1784, 1785} Topically, cortisone and hydrocortisone caused a decrease in the number of macrophages, giant cells and neutrophils, and a reduction in number and rounding up of the fibroblasts.^{81, 551, 1785}

Hydrocortisone impaired the ability of the cells to produce the leukocytosispromoting factor and probably leukotaxine. The mechanisms of resistance that are adversely affected by ACTH and cortisone were reviewed. Because of the severe exacerbation and destruction of tissue that occurred in infectious arthritis after withdrawal of cortisone which had suppressed the symptoms, Biström ¹⁸² warned against the uncritical use of cortisone. [We agree.—Ed.]

The action of hormones on the metabolism of mucopolysaccharides in connective tissues was reviewed by Dorfman.⁵⁴³

In tissue cultures, hydrocortisone, alcohol and desoxycorticosterone caused marked reversible inhibition of growth of chick embryo heart and gastrointestinal fibroblasts while allowing abundant growth of gastrointestinal epithelial cells, whereas cortisone acetate caused only slight inhibition. S45 In fibroblast cultures, desoxycorticosterone acetate and glucoside and compound S caused an increase in the size of cells and nuclei and in the tendency to lay down fibers. T77

Corticosterone and hydrocorticosterone in adrenalectomized rats increased the concentration of erythroid cells and decreased that of eosinophils and of lymphocytes in the bone marrow.⁷⁸¹ In synovial tissue incubated with cortisone and hydrocortisone, many of the nuclei were pyknotic.¹¹⁸² Intradermal or systemic cortisone, hydrocortisone and ACTH and, in some cases, hypophysectomy increased the number of abnormal mast cells.^{63, 1936, 1936, 2283} [The discrepancies between various studies indicate the difficulty in evaluating the relationship between mast cells and the pituitary-adrenal axis. This is a promising field for future research.—Ed.]

The inhibitory effect of intramuscular cortisone acetate on limb regeneration in the newt was postulated as being on the mitotic activity of cells and not on migratory activity. However, with intraperitoneal administration in newts no retardation of limb regeneration or difference in "mitotic activity" was found. The reason for the different effects was not apparent. In mice, cortisone inhibited the development of skin papillomas and caused regression of manifest tumors. In the difference may be due to action on mast cells is not supported by evidence.—Ed.] Cortisone also decreased the uptake of State in the mast cells in the papillomas. Hydrocortisone acetate given intraperitoneally in rabbits inhibited the formation of adhesions produced in controls by tale, or by removing areas of serosa or adhesions. There was no evidence to support any theory as to the mechanism.—Ed.

In rat tissue slices, hydrocortisone was bound by diaphragm, kidney and spleen as well as by liver, but the latter had much greater ability to degrade the steroid. 1247 Cortisone and pituitary growth hormone were antagonistic in their effect on capillary resistance. 1163, 2221 The eosinophil level in dogs was found to be twice as sensitive to cortisone as was the capillary resistance. 2220 An inverse relationship between eosinophil level and capillary resistance was present with a change in cortisone level or with a constantly high level, but not with a persistently low level of cortisone. 1162 No difference in capillary permeability to fluid, protein or sucrose was found in perfused hindquarters in normal or adrenalectomized rats, and no change was produced by adrenal cortical extract. 1720

EXPERIMENTAL ARTHRITIS

Bacterial. Pleuropneumonia organisms, widely dispersed in nature as various species (some pathogenic, others saprophytic), needed to be differentiated from "L-phase" variants of certain bacteria. The terminology for these variants was confusing [We agree.—Ed.], but the evidence that pleuropneumonia organisms caused disease in cattle was considered to be more definite than it was

in man. Edward agreed with previous evidence that these organisms were not the cause of nonspecific urethritis in man. [There is good evidence that pleuro-pneumonia-like organisms (so called L-organisms) are pathogenic in man.—Ed.]

Consistent production of a progressive arthritis in rats injected with L₄ strain of pleuropneumonia organisms was confirmed ¹⁵⁰⁴ in a study of various

gold preparations.

Sensitizing Agents. Guinea pigs and other animals receiving a wide variety of substances, such as cortisone, histamine, an induced infection, a number of mucoproteins and polysaccharides and trypsin, had distinctive but nonspecific lesions of connective tissue structure of the heart and joints which were apparently due to reaction to a variety of foreign substances and experimental technics, although the mechanism remained unknown. In these experiments there was no direct proof or disproof of its hypersensitiveness as the pathogenic mechanism, but certain aspects suggested that the earliest changes occurred before the expected development of tissue sensitivity or circulating antibodies. Anaphylactic (Arthus) arthritis was suppressed by whole egg yolk, and certain fractions thereof, given as dietary supplement for three or more weeks to baby guinea pigs, 398 and by appropriate administration of sodium salicylate, cortisone (or hydrocortisone) or splenin A. 394 The findings might be pertinent to the genesis of the rheumatic state, especially rheumatic fever. 393

Repeated intra-articular injections of histamine in various animals (rats, mice, hamsters and guinea pigs) produced connective tissue changes similar to those seen in human rheumatic diseases. With continued injections of histamine the changes in the fibrous connective tissue resembled many of those seen in fibrosis and early amyloidosis. The changes were considered to be mediated through an initially increased secretion of adrenocortical and gonadal steroids, and later failure or reduction of secretion of these hormones. [Few histologic studies of the effects of histamine upon connective tissues have been published. These observations offer an interesting new approach in the field.—Ed.] Even a single injection of certain exudates from granulomatous or tumoral tissues (lymphosarcoma) into rats resulted in a chronic and probably nonspecific hyperergic type of inflammatory reaction structurally resembling rheumatoid arthritis. 1084 In these animals a chronically inflamed synovial membrane was shown to proliferate and extend pannus-like across and to erode articular cartilage.

The severity of alterations in vascular and lymphoid tissue, but not of valvular and renal lesions, was reduced by prior sensitization of rabbits with small doses of either homologous or cross-reactive antigen. The presence of plasma cells in mesenchymal tissues in experimentally induced hypersensitivity reactions (by giving horse serum intravenously) and in collagen diseases indicated antibody formation. 1400

Hormonal Production and Influence. Hormonal and articular interrelationships were emphasized by a series of experiments using two specialized strains of male mice, one characterized by comparatively "active" (DBA strain) and the other by "inactive" thyroid glands (C57BL strain). 1890, 1901, 1902, 1908, 1004 ACTH given to male mice (C57BL strain) decreased the incidence and severity of degenerative joint disease, whereas a high-fat diet increased the incidence and advanced the onset. 1901

Radiothyroidectomy with I¹³¹ reversed the effect of a high-fat diet in these two strains, ^{1902, 1904} though this procedure at age six months without the high-fat diet produced a "characteristic athyroid joint disease" more often in the strain of animals with relatively active thyroid glands (DBA strain) than in those with relatively inactive thyroids (C57BL strain). [It was not claimed that "athyroid joint disease" in certain highly bred strains of mice was equivalent to human degenerative joint disease; in fact, certain differences were noted. ¹⁸⁹⁰—Ed.]

High-fat diet increased the incidence of degenerative joint disease in both spayed and unspayed female mice, but when these mice (C57BL strain) were spayed at three to four weeks of age, degenerative joint disease occurred less frequently and was retarded in onset. Experimental degenerative joint disease also was decreased or retarded by orchidectomy, and by adrenal or ovarian but not by anterior hypophysial grafts. 1900

Cortisone inhibited and aldosterone aggravated an anaphylactoid reaction in rats.¹⁰³⁴ Intra-articular injection of hydrocortisone into knee joints of rabbits, previously inflamed by injections of oil of turpentine or talc, exerted only a slightly "favorable influence on recovery." ¹⁶⁰⁴

Scorbutic and Nutritional. In guinea pigs with acute scurvy induced two weeks previously, administration of cortisone in doses two to four times a comparable clinical maintenance dose for human beings prevented changes in cardiac valves; changes were not prevented when cortisone was administered simultaneously with the scorbutogenic diet.¹⁰⁶⁵

Lathyrus odoratus seeds, ¹⁶⁵¹ or their active ingredient, α-amino-propionitrile, ²¹⁷⁶ incorporated in the diet of rats, produced within two weeks degenerative arthritis, other skeletal changes, and dissecting aortic aneurysm, thought to be due either to defective formation or to excessive destruction of chondroitin sulfate of the ground substance. ¹⁶⁵¹

Preparations of hypophysial growth hormone (STH) in thyroparathyroidectomized rats induced periarteritis nodosa and arthritic lesions, whereas this hormone in the intact rat did not cause these lesions. 1808

Other. A polyvinyl plastic was used successfully for a year in experimental arthroplasty on the knees of dogs, but was less satisfactory when the joint surfaces had previously been damaged. [We agree that repair in such instances may differ from the process in man.—Ed.]

SPONTANEOUS ARTHRITIS IN ANIMALS

In swine, naturally occurring erysipelas with arthritis was caused by Erysipelothrix rhusiopathiae; 1897 cortisone produced "marked clinical improvement" in three advanced chronic cases. 1898 [The relationship, if any, of this disease to human chronic arthritis is still questionable.—Ed.] Chronic tenosynovitis, tenovaginitis, bursitis and arthritis in chickens were due to a virus similar to rickettsia and distinct from pleuropneumonia organisms. 1225 An articular lesion similar to pigmented villonodular synovitis was induced in the knees of dogs during a year of repeated intra-articular injections of autogenous blood, but attempts to produce a comparable lesion in the Achilles tendon were unsuccessful. 2273

Severe osteoarthritis of the left hip, found in the skeletons of two gorillas, was attributed to previous Legg-Perthes' disease.²⁰⁶⁹ Arthritis developed in a colony of baboons: in one animal it was described as "arthritis deformans," and

occurred in conjunction with severe amyloidosis; in another, the arthritic changes affected both wrist joints. [These case reports lacked sufficient details to establish the type of arthritis.—Ed.]

THE CAMPAIGN AGAINST RHEUMATISM

The campaign against rheumatism in recent years has shown growth, with an increase in membership of organizations devoted to the cause of arthritis and rheumatism, and increasing funds available to these organizations for public education, research and patient care. The flow of new ideas resulting from research and clinical investigation may be measured to some degree by the number of papers included in this Review. In the Tenth Rheumatism Review, covering the six years from 1946 through 1951, 2,256 papers were included. In the Eleventh Review, covering a span of only three years, 2,325 were included.

New Journals. January, 1958, saw the launching of the first issue of the journal, Arthritis and Rheumatism, the official publication of the American Rheumatism Association. This was an event of historic significance, for it is the first journal devoted exclusively to the rheumatic diseases to appear in the United States. [In the short span of three years, three new journals devoted to the rheumatic diseases have appeared: Acta Rheumatologica Scandinavica (Scandinavia, 1955), Arthritis and Rheumatism (North America, 1958), and Archives of Inter-

American Rheumatology (South America, 1958).-Ed.]

World and National Organizations. A campaign is a matter of men, money, motives and deeds. The men engaged in the campaign against rheumatism have organized several associations. La Ligue Internationale Contre le Rheumatisme, formed in 1928,¹ has served well as an international forum for the exchange of ideas and information. The Ninth International Congress on Rheumatic Diseases, under the auspices of La Ligue, was conducted by the Canadian Rheumatism Association, with the assistance of the Canadian Arthritis and Rheumatism Society. It was held in Toronto, Ontario, Canada, from June 23 to June 28, 1957. This Congress was attended by over 1,000 physicians and scientists from 44 different countries, who heard approximately 200 papers concerned with various aspects of the rheumatic diseases.

The European League has held Congresses in Barcelona in 1951 and The Hague in 1955, and another has been planned for Istanbul in 1959. The Pan American League held its first Congress in Rio de Janeiro and Sao Paulo, Brazil, in 1955, and is arranging a second one to be held in the United States at Bethesda.

Maryland, in June, 1959.

Also in the international sphere, the World Health Organization presented the first Technical Report of its Expert Committee on Rheumatic Diseases in 1954 under the chairmanship of Dr. W. S. C. Copeman.²²⁸⁶ In this report the chronic rheumatic diseases were described as a neglected public health problem from both the medical and the research viewpoint, despite their social and economic significance. It also emphasized the need for improved nomenclature and classification in this group of diseases, and stressed that existing data on the incidence and prevalence of chronic rheumatic diseases were not adequate for the purposes for which morbidity statistics were commonly used.

In Britain, the Empire Rheumatism Council, established in 1936, has continued to press for improvements in the United Kingdom, and stimulated the

profession and government in New Zealand 500 to establish a rheumatism center. In England, the Council has sought recognition of rheumatism as a specialty field of medicine. 702 The rheumatism centers in England have already been itemized in the previous Rheumatism Review.1 The death of Lord Horder was a great loss to the specialty of physical medicine, and to the cause of rheumatic diseases in particular. He had been President of the British Association of Physical Medicine since it was founded in 1943 44, 45 and a respected and admired leader in the Empire Rheumatism Council.

In the United States, the American Rheumatism Association expanded its membership from 1,100 in 1955 to 1,226 in 1957. The Association, in addition to its regular annual spring scientific meetings, sponsored an Interim Session each fall. The first Interim Session in 1954 and the three subsequent meetings through 1957 were held at the National Institutes of Health in Bethesda, Maryland. This additional session provided a much needed opportunity for the presentation of papers dealing largely, though not exclusively, with laboratory research in the rheumatic diseases.

In the United States, the National Institute of Arthritis and Metabolic Diseases (NIAMD), established in 1950, continued its program of research and education.982 [The budget for the NIAMD of the U. S. Public Health Service for 1957 approximated \$20,000,000, and represented an increase of 28% over the funds for the same purpose in the preceding year; the total budget for NIAMD for 1954 was somewhat over \$7,000,000. These funds support the broad program of this Institute in its investigations of the metabolic as well as the rheumatic diseases. In the extensive laboratories and clinical facilities at the Clinical Center in Bethesda, Maryland, a research staff of able investigators are contributing knowledge in the broad field of the rheumatic diseases. Funds from this Institute also support the extramural programs by grants-in-aid and training grants to universities for the improvement of facilities and assistance in the education of physicians in both the basic and the clinical aspects of the connective tissue diseases. In addition, grants are made to investigators for projects after approval by "study sections" composed of scientists qualified in the various disciplines basic to the medical and biologic sciences. In this way, the Federal Government has expended these large appropriations on the basis of scientific merit, and only after the proposed research and the ability of the project personnel have been recommended by a competent nongovernmental advisory group. The educational and research institutions which have been recipients of such grants are free from objectionable limitations, and generally regard these contracts as highly desirable.—Ed.]

Several useful and instructive conferences held during the year 1956-1957 and sponsored jointly by the National Institute of Arthritis and Metabolic diseases, the Arthritis and Rheumatism Foundation and the American Rheumatism Association, attest to the effective integration of activities of these three national organizations in this country. The Second National Conference on Research and Education was held in Bethesda in December, 1956.295 The first National Conference on Serological Reactions in Rheumatoid Arthritis was held in New York in January, 1957, and the first International Conference on Population Studies in Rheumatoid Arthritis convened in Bethesda in June, 1957, immediately prior to the Ninth International Congress. Transactions of each of these conferences

have been published.

Arthritis Foundations. The Arthritis and Rheumatism Foundation, under the continued guidance of its Chairman, Mr. Flyd B. Odlum, and its President. General George C. Kenney, has increased its annual fund collection from \$1,771,458 in 1954–55 to \$2,220,017 in 1955–56,1,2207,2208 A large portion of this money has been allocated in the fields of research, public and professional education, clinical care, and direct service to arthritis patients. The Foundation awarded 29 research fellowships in the amount of \$156,000 for the year 1956–57.205 The distribution of several publications to physicians has been made possible by the Arthritis and Rheumatism Foundation; they include the Bulletin on Rheumatic Diseases, the Rheumatism Review, the Primer on Rheumatic Diseases, and a manual for nurses and physical therapists on the care of rheumatic patients. In 1957 the Foundation assembled and distributed, in this country and abroad, 250 teaching sets of 100 slides illustrating characteristic pathologic changes (gross and microscopic) in the various rheumatic diseases.

The Canadian Arthritis and Rheumatism Society (CARS) ^{229, 320, 360, 567, 600, 1646, 2012} functions in a manner analogous to that of the Arthritis and Rheumatism Foundation. In 1955 this organization collected over \$806,000, of which more than one-half went for direct patient services. A grant of \$500,000, provided by Mr. James A. Gairdner, a Toronto industrialist, and announced during the Ninth International Congress on Rheumatic Diseases, establishes a system of awards for outstanding work in the field of rheumatic and heart diseases. Under the terms of the grant, a prize of \$25,000 may be awarded as often as every four years, with three to five annual awards of not less than \$3,000 or more than \$10,000.

Increasing Interest in Rehabilitation. In the area of rehabilitation, the National Rehabilitation Association 1516 and the International Society for the Welfare of Cripples 74, 1798 have continued to point out the value of attempts to return disabled individuals to some form of employment. At the Seventh World Congress of the International Society for the Welfare of Cripples, held in London in 1957, a committee was appointed to study the feasibility of forming an international body for the dissemination and integration of knowledge on the rheumatic diseases in spheres other than those embraced by the Ligue Internationale. As mentioned by Rusk, 1799 the cost of rehabilitation may often be less than that of chronic public assistance. In some areas, rehabilitation centers have been organized at the local level and conducted by community support. 1414, 1707 Increasing attention has been directed to the employment problems of the crippled individual in the older age group, 1409 homecraft for the handicapped, 161 and aids for housekeeping for housewives with rheumatic diseases. 1165 A hospital for the management of long-term illness in older people was recently opened in Cleveland, Ohio. 365 Of the first 86 patients discharged from this hospital, five had rheumatoid arthritis and 13 osteoarthritis, and all retained the functional improvement acquired while in the hospital and justified the undertaking. The program was found to be greatly dependent upon a vigorous medical social service organization.

In general, the campaign against rheumatism has progressed satisfactorily and has achieved significant gains. Sir William Osler said in 1902: "To prevent disease, to relieve suffering and to heal the sick, this is our work." If these aims are to be reached for the arthritic, much yet remains to be done. Only preliminary efforts have been made in a few countries to determine the prevalence of such a relatively common disease as rheumatoid arthritis. Only

about 700 free hospital beds and about 276 special clinics were available in 1957 2208 for arthritis patients in the United States. In view of the enormous upsurge of enthusiasm and ultrascientific endeavor in the field of the rheumatic diseases, the comments offered by John P. Currie, 460 who characterized himself as "an elderly member of the profession," are worthy of consideration. He wrote: "It seems to me just as likely that progress in the understanding and treatment of rheumatic diseases will come from someone standing well back and surveying the whole problem as from someone peering through a powerful microscope at one small section of it. By all means let us research into colloid chemistry and peripheral antiphlogistic corticoid conditioners; let us analyze our results and use our laboratories; but let us also remember the importance of looking at our patients and their disease."

BIBLIOGRAPHY

- Rheumatism Reviews: (a) First, Ann. Int. Med. 8: 1315, 1495, 1673, 1935. (b) Second, Ibid. 9: 883, 1936. (c) Third, Ibid. 10: 754, 1936. (d) Fourth, Ibid. 11: 1089, 1938. (e) Fifth, Ibid. 12: 1005, 1295, 1939. (f) Sixth, Ibid. 13: 1655, 1937, 1940. (g) Seventh, Ibid. 14: 1383, 1631, 1941. (h) Eighth, Ibid. 15: 1002, 1941. (i) Ninth, Ibid. 28: 66-168, 309-451, 1948. (j) Tenth, Ibid. 39: 497-618, 758-906, 1953. (k) Eleventh, Ibid. 45: 831-945, 1060-1219, 1956.
- Abbott, W. E., Krieger, H., and Levey, S.: The role of ACTH, cortisone and hydrocortisone in surgery, Ann. Int. Med. 43: 702 (Oct.) 1955.
- 3. Abdin, F. H.: Tumors of synovial origin, North Carolina M. J. 16: 210 (June) 1955.
- Abraham, A.: Innervation of the connective tissue, Acta Morphol. Hung. 4: 125, 1954.
- Abrams, H. L., Carnes, W. H., and Eaton, J.: Alimentary tract in disseminated scleroderma with emphasis on small bowel, Arch. Int. Med. 94: 61 (July) 1954.
- Abrams, W. B., and Chesley, G. L.: The ballistocardiogram in acute rheumatic fever, Circulation 9: 400 (Mar.) 1954.
- Adams, F. H.: Newer concepts in the diagnosis and treatment of rheumatic fever, J. A. M. A. 156: 1319 (Dec. 4) 1954.
- Adams, J. L.: The familial occurrence of lupus erythematosus, New Zealand M. J. 53: 504 (Oct.) 1954.
- 9. Adams, J. P.: Knee pain, GP 11: 95 (May) 1955.
- 10. Adkins, E. W. O.: Spondylolisthesis, J. Bone and Joint Surg. 37B: 48 (Feb.) 1955.
- Adler, E., and Magora, A.: Experiments on the relation between short wave irradiation and the pituitary-cortico-adrenal system, Am. J. Phys. Med. 34: 521 (Oct.) 1955.
- Adler, E., and Maybaum, S.: Rare features in a case of Gaucher's disease, Ann. Rheumat. Dis. 13: 229 (Sept.) 1954.
- Adlersberg, D., Stricker, J., and Himes, H.: Hazard of corticotropin and cortisone therapy in patients with hypercholesteremia, J. A. M. A. 159: 1731 (Dec. 31) 1955.
- Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., and Bates, G.: Plasma thromboplastin component (PTC) deficiency: a new disease resembling hemophilia, Proc. Soc. Exper. Biol. and Med. 79: 692 (Apr.) 1952.
- Aikawa, J. K., and Rhyne, M. B.: The effect of prolonged corticotropin therapy for rheumatic fever on the exchangeable sodium content and body weight, Circulation 12: 891 (Nov.) 1955.
- Aikawa, J. K.: Hypersensitivity and rheumatic fever, Ann. Int. Med. 41: 576 (Sept.) 1954.

- Aikens, R. L., and Beckwith, C. J. W.: Sarcoidosis: improvement in chest x-ray shadows during pregnancy, Dis. of Chest 28: 580 (Nov.) 1955.
- Ainger, L. E., Ely, R. S., Done, A. K., Brill, A. B., and Kelley, V. C.: Sydenham's chorea. I. Evidence of abnormal adrenal cortex function, Am. J. Dis. Child. 89: 575 (May) 1955.
- Ainger, L. E., Ely, R. S., Done, A. K., and Kelley, V. C.: Sydenham's chorea. II. Effects of hormone therapy, Am. J. Dis. Child. 89: 580 (May) 1955.
- Akamine, R. N., Engel, M. B., and Sarnat, B. G.: Histochemical studies of cartilage implants, J. Bone and Joint Surg. 36A: 1166 (Dec.) 1954.
- Albanese, A. A., Higgons, R. A., Avery, W. G., and Dilallo, R.: The effect of salicylates on the vitamin C stores of rheumatic fever patients, New York State J. Med. 55: 1167 (Apr. 15) 1955.
- Albert, S. M., Rechtman, A. M., and Kremens, V.: The significance of spinal fluid protein level in intervertebral disk pathology, Pennsylvania M. J. 58: 1235 (Nov.) 1955.
- Aldes, J. H., Jadeson, W. J., and Grabinski, S.: A new approach to the treatment of subdeltoid bursitis, Am. J. Phys. Med. 33: 79 (Feb.) 1954.
- Aldes, J. H., and Klaras, T.: Use of ultrasonic radiation in the treatment of subdeltoid bursitis with and without calcareous deposits. West. J. Surg. 62: 369 (July) 1954.
- Alexander, M. K., and Cope, S.: Erythema multiforme exudativum major (Stevens-Johnson syndrome), J. Path. and Bact. 68: 373 (Oct.-Nov.) 1954.
- Alexander, R., and deForest, G. K.: The sensitized sheep cell agglutination reaction in rheumatoid arthritis, Am. J. Med. 16: 191 (Feb.) 1954.
- Alldred, A. J.: Dupuytren's contracture, Australian and New Zealand J. Surg. 24: 66 (Aug.) 1954.
- Allen, G. E., Rogers, F. B., and Lansbury, J.: Osteogenesis imperfecta tarda with hyperuricemia and gout, report of three cases, Am. J. M. Sc. 230: 30 (July) 1955.
- Allen, R. A., Woolner, L. B., and Ghormley, R. K.: Soft-tissue tumors on the sole, with special reference to plantar fibromatosis, J. Bone and Joint Surg. 37A: 14 (Jan.) 1955.
- Allison, F., Jr., Smith, M. R., and Wood, W. B., Jr.: Studies on the pathogenesis of acute inflammation. II. The action of cortisone on the inflammatory response to thermal injury, J. Exper. Med. 102: 669 (Dec.) 1955.
- Ameen, L.: Psychosomatic study of a case of palindromic rheumatism, J. Nerv. and Ment. Dis. 120: 253 (Sept.-Oct.) 1954.
- American Rheumatism Association Committee: Experience with cortisone in the management of rheumatoid arthritis, Ann. Rheumat. Dis. 14: 325 (Dec.) 1955.
- Amprino, R.: Autoradiographic research on the S^{ss}-sulphate metabolism in cartilage and bone differentiation and growth, Acta anat. 24: 121, 1955.
- 34. Amprino, R.: On the incorporation of radiosulfate in the cartilage, Experientia 11: 65 (Feb.) 1955.
- Anderson, A. E., Jr.: Suppression of the manifestation of gout with continuous cortisone therapy, Am. J. Med. 16: 292 (Feb.) 1954.
- Anderson, J., Harper, C., Dent, C. E., and Philpot, G. R.: Effect of cortisone on calcium metabolism in sarcoidosis with hypercalcaemia, Lancet 2: 720 (Oct. 9) 1954.
- Anderson, T. P.: Management of degenerative joint disease of the knee, Arch. Phys. Med. 36: 154 (Mar.) 1955.
- 38. Andersson, E.: Allergic polyarthritis, Acta Allergol. 7: 409, 1954.
- Andrew, J.: Sacralization: an aetiological factor in lumbar intervertebral disk lesions, and a cause of misleading focal signs, Brit. J. Surg. 42: 304 (Nov.) 1954.
- 40. Anonymous: Classification of rheumatic diseases, Rheumatism 10: 96 (Dec.) 1954.

- Anonymous: The effect of the administration of ACTH and cortisone on the sedimentation rate and fibrinogen levels, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 33.
- 42. Anonymous: Fludrocortisone acetate, J. A. M. A. 159: 1539 (Dec. 17) 1955.
- 43. Anonymous: Gout, M. Times, New York 83: 451 (May) 1955.
- 44. Anonymous: Lord Horder, obituary, Ann. Phys. Med. 2: 273 (Oct.) 1955.
- 45. Anonymous: Lord Horder, Medicine Illus., London 9: 591 (Sept.) 1955.
- Anonymous: Mobile services at work, reports from various centres, Brit. J. Phys. Med. 18: 245 (Nov.) 1955.
- 47. Anonymous: Stenosing tenosynovitis, M. Times, New York 82: 421 (June) 1954.
- 48. Antes, E. H.: Charcot joint in diabetes mellitus, J. A. M. A. 156: 602 (Oct. 9) 1954.
- Anwyl-Davies, T.: Articular and non-articular rheumatic complications of venereal disease, Brit. J. Phys. Med. 18: 170 (Aug.) 1955.
- Appleby, J. I., and Norymberski, J. K.: Urinary excretion of 17-hydroxy-20oxosteroids in normal health and in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 172 (June) 1955.
- Arbeit, S. R., Dolan, M. A., and Stollerman, G. H.: Ballistocardiographic study of body acceleration during the acute and convalescent stages of rheumatic fever, Am. Heart J. 49: 647 (May) 1955.
- Archer, B. H., and Kantor, M. G.: Agranulocytosis with recovery following the use of phenylbutazone (Butazolidin), New York State J. Med. 54: 394 (Feb.) 1954.
- Ardan, N. I., Jr., Janes, J. M., and Herrick, J. F.: Changes in bone after exposure to ultrasonic energy, Minnesota Med. 37: 415 (June) 1954.
- Arden, G. P.: The value of phenylbutazone in orthopaedic conditions, Rheumatism 10: 44 (Apr.) 1954.
- Arendt, E. C., Pattee, C. J., and Mitchell, H. S.: Calcinosis universalis, Canad. M. A. J. 73: 269 (Aug. 15) 1955.
- Arje, S. L., and Bachman, K. B.: Disseminated lupus erythematosus and pregnancy, Obst. and Gynec. 4: 524 (Nov.) 1954.
- Arner, S.: Spontaneous circumscribed panniculitis (Weber-Christian disease), Acta dermat.-venereol. 34: 194, 1954.
- Arnold, J. G., Jr.: The clinical manifestations of spondylochondrosis (spondylosis) of the cervical spine, Ann. Surg. 141: 872 (June) 1955.
- Aronoff, A., Bywaters, E. G. L., and Fearnley, G. R.: Lung lesions in rheumatoid arthritis, Brit. M. J. 2: 228 (July 23) 1955.
- Aronsson, H.: The prognosis of acute suppurative infection of the flexor tendon sheaths of the hand, Acta chir. Scandinav. 109: 58, 1955.
- Arosenius, K. E.: Vertebral fracture in pelvo-spondylitis ossificans (Mb Bechterew), Acta Soc. Med. Upsal. 59: 238 (Mar.) 1954.
- 62. Arvidsson, H., and Johansson, O.: Arthrography of the elbow-joint, Acta radiol. 43: 445 (June) 1955.
- Asboe-Hansen, G.: Autoradiographic evidence of cortisone action on mast cells in experimental skin tumors, Cancer Research 14: 94 (Feb.) 1954.
- 64. Asboe-Hansen, G., and Zachariae, L.: Mast-cell changes induced by hydrocortisone acetate in experimental skin papillomas in mice, Acta path. et microbiol. Scandinav. 37: 145, 1955.
- Ascenzi, A., and Chiozzotto, A.: Electron microscopy of the bone ground substance using the pseudo-replica technique, Experientia 11: 140 (Apr.) 1955.
- Ascenzi, A.: Some histochemical properties of the organic substance in Neanderthalian bone, Am. J. Phys. Anthropol. n. s. 13: 557 (Dec.) 1955.
- Ascenzi, A.: The structure of bone tissue as studied in the electron microscope, Sc. Med. ital. 3: 670, 1955.

- Ashley, G. T.: The morphological and pathological significance of synostosis at the manubrio-sternal joint, Thorax 9: 159 (June) 1954.
- Atkins, E., Allison, F., Jr., Smith, M. R., and Wood, W. B., Jr.: Studies on the antipyretic action of cortisone in pyrogen-induced fever, J. Exper. Med. 101: 353 (Apr.) 1955.
- d'Aubigné, R. M., and Postel, M.: Functional results of hip arthroplasty with acrylic prosthesis, J. Bone and Joint Surg. 36A: 451 (June) 1954.
- Aune, S.: Osteo-arthritis in the first carpo-metacarpal joint, Acta chir. Scandinav. 109: 449, 1955.
- Austen, F. K., and Clakins, E.: Serial studies of synovial fluid in evaluating intraarticular agents, Ann. Rheumat. Dis. 14: 283 (Sept.) 1955.
- Austrian, C. R., and Boger, W. P.: Sensitization and subsequent desensitization to probenecid (Benemid), Arch. Int. Med. 98: 505 (Oct.) 1956.
- Bach, F.: International Society for the Welfare of Cripples, Sixth World Congress, Ann. Phys. Med. 2: 182 (Jan.) 1955.
- Bach, F.: The management of the rheumatic patient, Brit. J. Phys. Med. 18: 202 (Sept.) 1955.
- Bachman, K. P., and Rogers, C. E.: Perforated gastric ulcer and gastrocolic fistula associated with prolonged cortisone therapy, U. S. Armed Forces M. J. 6: 109 (Jan.) 1955.
- Badgley, C. E.: Use of compound F in common lesions of the upper extremity, J. Michigan M. Soc. 54: 1088 (Sept.) 1955.
- Badin, J., Schubert, M., and Vouras, M.: Plasma polysaccharide fraction containing uronic acid, in normal subjects and in patients with rheumatoid arthritis, J. Clin. Investigation 34: 1317 (Aug.) 1955.
- Badin, J., and Glyn, J.: Relationship between plasma mucoproteins and protein sugar in patients with rheumatoid arthritis receiving cortisone, Proc. Soc. Exper. Biol. and Med. 86: 150 (May) 1954.
- Baeder, D. H., and Seifter, J.: Effect of adrenalectomy and hypophysectomy in permeability of the synovial membrane in rabbits, Proc. Soc. Exper. Biol. and Med. 87: 280 (Nov.) 1954.
- Baeder, D. H., Glassman, J. M., Hudyma, G. M., and Seifter, J.: Effect of hyaluronidase and partially depolymerized hyaluronate on threshold doses of drugs, Proc. Soc. Exper. Biol. and Med. 89: 645 (Aug.) 1955.
- Bagnall, A. W.: A new technique for the local use of hydrocortisone in rheumatic disease, Canad. M. A. J. 73: 972 (Dec. 15) 1955.
- Bagnall, A. W.: The value of chloroquine in rheumatoid disease, a four-year study of continuous therapy, Canad. M. A. J. 77: 182 (Aug. 1) 1957.
- Baird, J. P.: Discussion of some aspects of ankylosing spondylitis. Proc. Roy. Soc. Med. 48: 201 (Mar.) 1955.
- Baker, B. L.: The connective tissue reaction around implanted pellets of steroid hormones, Anat. Rec. 119: 529 (Aug.) 1954.
- Baker, D. M.: Changes in the corium and subcutaneous tissues as a cause of rheumatic pain, Ann. Rheumat. Dis. 14: 385 (Dec.) 1955.
- Baker, F.: Physical medicine in treatment of degenerative joint diseases, J. A. M. A. 157: 492 (Feb. 5) 1955.
- Baker, L. D.: The diagnosis and care of Marie-Strümpell arthritis, Postgrad. Med. 15: 428 (May) 1954.
- Baker, W. H.: Aortitis and aortic valve disease in rheumatoid arthritis, Am. Pract. and Digest Treat. 6: 1236 (Aug.) 1955.
- Ball, J.: Differential agglutination test in rheumatoid arthritis complicated by pneumoconiosis, Ann. Rheumat. Dis. 14: 159 (June) 1955.
- Ball, J.: Rheumatoid arthritis and polyarteritis nodosa, Ann. Rheumat. Dis. 13: 277 (Dec.) 1954.

- Ballabio, C. B., Sala, G., and Amira, A.: Topical hydrocortisone in pleuropericardial exudations, Dis. of Chest 27: 190 (Feb.) 1955.
- Banfield, W. G.: Width and length of collagen fibrils during the development of human skin, in granulation tissue and the skin of adult animals, J. Gerontol. 10: 13 (Jan.) 1955.
- Banghart, H. E., and Warter, P. J.: d-Amphetamine sulfate as an adjunct to the treatment of rheumatic diseases, Am. Pract. and Digest Treat. 5: 867 (Nov.) 1954.
- Banghart, H. E.: A clinical evaluation of methyl androstenediol in the treatment of osteoporosis, Am. Pract. and Digest Treat. 5: 964 (Dec.) 1954.
- Bangle, R., Jr., and Alford, W. C.: The chemical basis of the periodic acid Schiff reaction of collagen fibers with reference to periodate consumption by collagen and by insulin, J. Histochem. and Cytochem. 2: 62 (Jan.) 1954.
- Bank, N.: The relation of malignant hypertension to periarteritis nodosa in humans,
 J. Mt. Sinai Hosp. 22: 290 (Nov.) 1955.
- Barden, F. W., Hill, P. S., and Cuneo, K. J.: Evaluation of a drug therapy in arthritis and rheumatoid conditions, J. Maine M. A. 46: 99 (Apr.) 1955.
- Barkin, R. E., Stillman, J. S., and Potter, T. A.: The spondylitis of juvenile rheumatoid arthritis, New England J. Med. 253: 1107 (Dec. 22) 1955.
- Barnett, C. H.: The structure and functions of fibro-cartilages within vertebrate joints, J. Anat. 88: 363 (July) 1954.
- 101. Baroody, W. G., and Shugart, R. T.: The simultaneous occurrence of duodenal and gastric ulcer during therapy with ACTH, Am. Pract. and Digest Treat. 6: 1876 (Dec.) 1955.
- 102. Barrow, J. G.: The choice of drugs in the prophylaxis of rheumatic fever, J. M. A. Georgia 44: 481 (Oct.) 1955.
- 103. Bartels, E. C.: Gout, Postgrad. Med. 15: 254 (Mar.) 1954.
- 104. Bartels, E. C.: Gout-now amenable to control, Ann. Int. Med. 42: 1 (Jan.) 1955.
- 105. Bartels, E. C.: Treatment of gout metabolism, Metabolism 6: 297 (May) 1957.
- 106. Bartels, E. D., Christensen, L. K., and Ohlsen, A. S.: Renal affection complicating scleroderma, Acta. path. et microbiol. Scandinav. Supp. 105: 174, 1955.
- Bartfeld, H.: Gout in a Negro woman, report of a case, J. A. M. A. 154: 335 (Jan. 23) 1954.
- 108. Bartfeld, H.: Use of reserpine in psychogenic rheumatism, osteoarthritis and rheumatoid arthritis, J. A. M. A. 159: 1510 (Dec. 17) 1955.
- 109. Bassiouni, M.: Studies of the acid polysaccharide of the white cells in rheumatic and other diseases showing its similarity to the acid polysaccharide of amyloid, Ann. Rheumat. Dis. 14: 288 (Sept.) 1955.
- 110. Bastow, J.: Some observations on the after-care of the arthritic patient, Physiotherapy 41: 273 (Sept.) 1955.
- 111. Bastow, J.: The surgery of rheumatic disease, Postgrad. M. J. 31: 635 (Dec.) 1955.
- Batch, J. W.: Measurements and recording of joint function, U. S. Armed Forces M. J. 6: 359 (Mar.) 1955.
- 113. Bate, T. H.: Hemangiomata of the tendon sheath, J. Bone and Joint Surg. 36A: 104 (Jan.) 1954.
- 114. Batterman, R. C., and Grossman, A. J.: Effectiveness of salicylamide as an analgesic and antirheumatic agent, evaluation of the double blindfold technique for studying analgesic drugs, J. A. M. A. 159: 1619 (Dec. 24) 1955.
- Bauer, G. E.: Scleroderma with heart failure, Australasian Ann. Med. 4: 149 (May) 1955.
- 116. Bauer, W., and Ropes, M. W.: Advances in the treatment of chronic rheumatic diseases, Practitioner 177: 431 (Oct.) 1956.
- 117. Bauer, W.: Diagnosis of gout, New England J. Med. 229: 583 (Oct. 7) 1943.
- 118. Bauer, W., and Klemperer, F.: The treatment of gout, New England J. Med. 231: 681 (Nov. 16) 1944.

- Bauwens, P., and Coyer, A. B.: The "multifidus triangle" syndrome as a cause of recurrent low-back pain. Brit. M. J. 2: 1306 (Nov. 26) 1955.
- Bavin, E. M., Drain, D. J., Seymour, D. E., and Waterhouse, P. D.: Anti-inflammatory compounds. I. The activity of a series of new compounds compared with phenylbutazone and cortisone, J. Pharm. and Pharmacol. 7: 1022 (Dec.) 1955.
- Bayles, T. B.: Bursitis and fibrositis, clinical and therapeutic aspects, M. Clin. North America 39: 1483 (Sept.) 1955.
- Bayles, T. B.: Cortisone, hydrocortisone and ACTH in rheumatic disease, Missouri Med. 51: 999 (Dec.) 1954.
- 123. Bayliss, R. I. S., and Steinbeck, A. W.: The adrenal response to corticotrophin, effect of ACTH on plasma adrenal steroid levels, Brit. M. J. 1: 486 (Feb. 27) 1954.
- 124. Bayliss, R. I. S., and Steinbeck, A. W.: Salicylates and the plasma level of adrenal steroids, Lancet 1: 1010 (May 15) 1954.
- 125. Bear, R. S.: Configuration of collagen and gelatin molecules in condensed and dispersed states, Soc. Exper. Biol. Gt. Brit. Symposia 9: 97, 1955.
- Beattie, J. W., and Hartfall, S. J.: Corticotrophin intravenous infusion therapy in rheumatic conditions, Brit. M. J. 1: 1494 (June 25) 1955.
- Beattie, J. W., and Woodmansey, A.: Radiation pain thresholds in relation to skin temperatures, Ann. Rheumat. Dis. 14: 397 (Dec.) 1955.
- 128. Beaumont, W.: Advances in physical medicine, Practitioner 175: 471 (Oct.) 1955.
- 129. Bechtol, C. O.: Coracobrachialis brevis, Clin. Orthop. 4: 152, 1954.
- Beck, J. C.: The present status of ACTH and adrenal steroid therapy in medicine, Ann. Int. Med. 43: 667 (Oct.) 1955.
- Beck, L.: Keratosis blennorrhagica or Reiter's syndrome?, New York State J. Med. 54: 1801 (June 15) 1954.
- Beck, W. C., and Berkheiser, S.: Prominent costal cartilages (Tietze's syndrome), Surgery 35: 762 (May) 1954.
- 133. Becker, I. M., and Shea, M. C.: Phenylbutazone toxicity, U. S. Armed Forces M. J. 5: 259 (Feb.) 1954.
- Beecher, H. K.: Appraisal of drugs intended to alter subjective responses, symptoms,
 J. A. M. A. 158: 399 (June 4) 1955.
- Beeman, E. A.: The importance of Coxsackie viruses, Practitioner 173: 551 (Nov.) 1954.
- Begg, A. C.: Nuclear herniations of the intervertebral disc: their radiological manifestations and significance, J. Bone and Joint Surg. 36B: 180 (May) 1954.
- Bélanger, L. F.: Autoradiographic visualization of Ca⁴⁶ intake by normal and pathological cartilage in vitro, Proc. Soc. Exper. Biol. and Med. 88: 150 (Jan.) 1955.
- 138. Bélanger, L. F.: Autoradiographic visualization of the entry and transit of S⁸⁵ in cartilage, bone, and dentine of young rats and the effect of hyaluronidase in vitro, Canad. J. Biochem. and Physiol. 32: 161 (May) 1954.
- 139. Bell, R. L.: Hemangioma of a dorsal vertebra with collapse and compression myelopathy, J. Neurosurg. 12: 570 (Nov.) 1955.
- Bendall, J. R.: The titration curves of elastin and of the derived a- and b-proteins, Biochem. J. 61: 31 (Sept.) 1955.
- 141. Benditt, E. P.: Histochemical observations on connective tissues, including a note on the use of chymotrypsin as a mucolytic agent for use in gastric lavage for cell studies, Texas Rep. Biol. and Med. 13: 623, 1955.
- 142. Benedek, T. G., and Montgomery, M. M.: The influence of ACTH and cortisone on the incidence of infections, J. Lab. and Clin. Med. 44: 766 (Nov.) 1954.
- 143. Benitez, H. H., Murray, M. R., and Chargaff, E.: Studies on inhibition of the colchicine effect on mitosis, Ann. New York Acad. Sc. 58: 1288 (Nov. 17) 1954.
- 144. Bennee, J.: Scleroderma treated with 2% procaine intravenously, Canad. M. A. J. 70: 71 (Jan.) 1954.

- 145. Bennett, G.: Uveitis, a clinical and statistical survey, Brit. J. Ophth. 39: 727 (Dec.) 1955.
- 146. Bennett, R. L., and Driver, M. F.: Role of occupational therapy in rehabilitation of the physically handicapped, Arch. Phys. Med. 36: 699 (Nov.) 1955.
- Bennett, W. A.: Histopathological alterations of adrenal and anterior pituitary glands in patients treated with cortisone, J. Bone and Joint Surg. 36A: 867 (July) 1954.
- 148. Bensley, S. H.: Some factors involved in histamine-induced arthritis and rheumatism in animals, First Canad. Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 61.
- Berenson, G. S., Roseman, S., and Dorfman, A.: A chromatographic method for the separation of acid mucopolysaccharides, Biochem. et Biophys. Acta 17: 75 (May) 1955.
- 150. Bergentz, S-E.: Ulceration of the stomach attending cortisone and corticotropin therapy, report of a case, Acta chir. Scandinav. 109: 334, 1955.
- Berger, H.: The treatment of postmyocardial infarction shoulder-hand syndrome with local hydrocortisone, Postgrad. Med. 15: 508 (June) 1954.
- 152. Bergmann, F., and Dikstein, S.: Studies on uric acid and related compounds. I. Quantitative determination of uric acid in biological fluids, J. Biol. Chem. 211: 149 (Nov.) 1954.
- 153. Bergsman, A., von Reis, G., and Sahlgren, F.: On the prognosis of brachialgia, Acta med. Scandinav. 151: 391, 1955.
- 154. Bernstein, H.: The current status of cortisone in post-operative treatment of Dupuytren's contracture, New York State J. Med. 54: 90 (Jan. 1) 1954.
- 155. Bernstein, S. H., Feldman, H. A., Harper, O. F., Jr., and Klingensmith, W. H.: Mass oral penicillin prophylaxis in control of streptococcal disease, Arch. Int. Med. 93: 894 (June) 1954.
- 156. Bernstein, S. H., Feldman, H. A., Harper, O. F., Jr., Klingensmith, W. H., and Cantor, J. A.: Observations in air force recruits of streptococcal diseases and their control with orally administered penicillin, J. Lab. and Clin. Med. 44: 1 (July) 1054
- Berris, H.: Tuberculous spondylitis simulating herniated intervertebral disk, Neurology 4: 710 (Sept.) 1954.
- 158. Besterman, E. M. M.: The cardiac output in acute rheumatic carditis, Brit. Heart J. 16: 8 (Jan.) 1954.
- Bettley, F. R.: The "L.E.-cell" phenomenon in active chronic viral hepatitis, Lancet 2: 724 (Oct. 1) 1955.
- Bevans, M., Nadell, J., Demartini, F., and Ragan, C.: The systemic lesions of malignant rheumatoid arthritis, Am. J. Med. 16: 197 (Feb.) 1954.
- 161. Beyer, M. F.: Homecraft for the handicapped, J. Rehabil. 20: 7 (July-Aug.) 1954.
- 162. Bhattacharyya, M.: Aetiology of rheumatic fever, J. Indian M. A. 24: 428 (Mar. 1) 1955.
- 163. Bianchi, C.: Further studies on compounds reducing synovial membrane permeability, Brit. J. Pharmacol. 9: 166 (June) 1954.
- 164. Bibawi, E., and Mahfouz, M. M.: Clinical evaluation of phenylbutazone (Butazoli-dine) in chronic rheumatic diseases, J. Egyptian M. A. 38: 342, 1955.
- 165. Bick, E. M.: Skeletal osteophytosis, J. Mt. Sinai Hosp. 22: 316 (Nov.-Dec.) 1955.
- Bick, E. M.: Vertebral osteophytosis, pathologic basis of its roentgenology. Am. J. Roentgenol. 73: 979 (June) 1955.
- 167. Bien, E. J., Yü, T. F., Benedict, J. D., Gutman, A. B., and Stetten, D., Jr.: The relation of dietary nitrogen consumption to the rate of uric acid synthesis in normal and gouty man, J. Clin. Investigation 32: 778 (Aug.) 1953.
- 168. Bien, E. J., and Zucker, M.: Uricolysis in normal and gouty individuals, Ann. Rheumat. Dis. 14: 409 (Dec.) 1955.

- Biering, A., and Iversen, T.: Osteogenesis imperfecta associated with Ehlers-Danlos syndrome, Acta paediat. 44: 279 (May) 1955.
- 170. Biggs, R., Douglas, A. S., MacFarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., and O'Brien, J. R.: Christmas disease, a condition previously mistaken for haemophilia, Brit. M. J. 2: 1378 (Dec. 27) 1952.
- Bilik, S. E.: Prevention of superimposed disabilities, New York State J. Med. 54: 1625 (June 1) 1954.
- 172. Bilka, P. J., and Weil, M. H.: Gold-hormonal therapy in rheumatoid arthritis, Ann. Int. Med. 42: 638 (Mar.) 1955.
- 173. Bilka, P. J.: A new hydrocortisone for intra-articular use, Minnesota Med. 38: 408 (June) 1955.
- Biörck, G., and Hall, P.: Follow-up studies in rheumatic fever patients, Acta Rheum. Scandinav. 1: 119, 1955.
- Biörck, G.: Rheumatic heart disease as a problem of preventive cardiology, J. Chron. Dis. 1: 591 (June) 1955.
- 176. Birke, G.: Studies on the neutral 17-ketosteroid excretion pattern in man, clinical and metabolic investigation with the aid of chromatographic separation and infrared spectrography, 1954, Södertörns Tryckeri, Stockholm.
- Birke, G., and Plantin, L.: Studies on urinary 17-ketosteroids, Acta med. Scandinav. Supp. 291, 1954.
- Bishop, C., and Pfaff, W.: Immediate uricosuric effect of probenecid in normal humans, Proc. Soc. Exper. Biol. and Med. 88: 346 (Mar.) 1955.
- 179. Bishop, C., Beyer, A., and Talbott, J. H.: Isotopic uric acid in gouty and rheumatoid arthritis patients treated with probenecid and phenylbutazone, Proc. Soc. Exper. Biol. and Med. 86: 760 (Aug.) 1954.
- 180. Bishop, C., Rand, R., and Talbott, J. H.: Rate of conversion of isotopic glycine to uric acid in the normal and gouty human and how this is affected by vitamin E and folic acid, Metabolism 4: 174 (Mar.) 1955.
- 181. Bishop, C., Zimdahl, W. T., and Talbott, J. H.: Uric acid in two patients with Wilson's disease (hepatolenticular degeneration), Proc. Soc. Exper. Biol. and Med. 86: 440 (July) 1954.
- Biström, O.: The injurious effect of cortisone on destructive inflammation, Acta chir. Scandinav. 109: 200, 1955.
- 183. Biström, O.: Need degenerative changes in the spinal column entail back pain?, Ann. chir. et gynaec. Fenniae 43: 29, 1954.
- 184. Biström, O.: Neuropathic joint disease and trauma, Ann. chir. et gynaec. Fenniae 43: Supp. 5: 40, 1954.
- Biström, O.: Sciatica cured by treatment of concurrent thyrotoxicosis, Acta chir. Scandinav. 106: 479, 1953.
- Biswas, S. K.: Generalised hypertrophic osteoarthropathy with gynaecomastia, J. Indian M. A. 25: 326 (Sept. 16) 1955.
- Björnesjö, K. B.: Staining of protein-bound serum polysaccharides in electrophoresis strips, Scandinav. J. Clin. and Lab. Invest. 7: 153, 1955.
- 188. Black, R. L., Lowney, J. F., and Duffy, P. M.: Alcaptonuria and ochronosis, report of five cases occurring in an American family, Arch. Int. Med. 93: 75 (Jan.) 1954.
- Blackett, N. M.: On the organisation of collagen fibrils in bone, Biochim. et Biophys. Acta 16: 161 (Jan.) 1955.
- 190. Blair, G. W. S., Williams, P. O., Fletcher, E. T. D., and Markham, R. L.: On the flow of certain pathological human synovial effusions through narrow tubes, Biochem. J. 56: 504 (Mar.) 1954.
- 191. Blake, J. A.: A homemade whirlpool bath, GP 11: 113 (Apr.) 1955.
- Blankenhorn, M. A., and Knowles, H. C.: Periarteritis nodosa: recognition and clinical symptoms, Ann. Int. Med. 41: 887 (Nov.) 1954.

- 193. Block, E. A.: Milton's gout, Bull. Hist. Med. 28: 201 (May) 1954.
- 194. Blockey, N. J., Wright, J. K., and Kellgren, J. H.: Oral cortisone therapy in periarthritis of the shoulder, Brit. M. J. 1: 1455 (June 26) 1954.
- Bloom, H. J. G., Ellis, H., and Jennett, W. B.: The early diagnosis of spinal tumours, Brit. M. J. 1: 10 (Jan. 1) 1955.
- 196. Blumberg, B.: The natural history of rheumatoid spondylitis, Bull. Rheumat. Dis. 6: 95 (Oct.) 1955.
- 197. Blumberg, B. S., Oster, G., and Meyer, K.: Changes in the physical characteristics of the hyaluronate of ground substance with alterations in sodium chloride concentration, J. Clin. Investigation 34: 1454 (Sept.) 1955.
- Blumberg, B. S., and Oster, G.: Light-scattering studies on hyaluronic acid, Science 120: 432 (Sept. 10) 1954.
- Boake, W. C., and Muir, H.: The non-antigenicity of chondroitin sulphate, Lancet
 1222 (Dec. 10) 1955.
- 200. Boas, N. F., Bollet, A. J., and Bunim, J. J.: Effect of acute clinical stress on the levels of hexosamine in serum and its excretion in urine, J. Clin. Investigation 34: 782 (June) 1955.
- Boas, N. F., and Foley, J. B.: Regulation of connective tissue hexosamine levels by the anterior pituitary and thyroid glands, Proc. Soc. Exper. Biol. and Med. 87: 89 (Oct.) 1954.
- 202. Boedtker, H.: On the nature of the structural element of collagen, J. Am. Chem. Soc. 77: 248 (Jan.) 1955.
- 203. Bogash, M., and Dowben, R. M.: Low protein diet in the management of recurrent uric acid stones, J. Urol. 72: 1057 (Dec.) 1954.
- 204. Bogdonoff, M. D., Shock, N. W., and Parsons, J.: The effects of stilbestrol on the retention of nitrogen, calcium, phosphorus, and potassium in aged males with and without osteoporosis, J. Gerontol. 9: 262 (July) 1954.
- 205. Boger, W. P., Strickland, S. C., Bayne, G. M., and Gylfe, J.: Probenecid and salicylates: the question of interaction in terms of penicillin excretion, J. Lab. and Clin. Med. 45: 478 (Mar.) 1955.
- 206. Boger, W. P., and Strickland, S. C.: Probenecid (Benemid) its uses and side-effects in 2,502 patients, Arch. Int. Med. 95: 83 (Jan.) 1955.
- 207. Boger, W. P., and Smith, R. T.: The role of probenecid in the therapy of gout, Svenska Lakartidningen 51: 2021 (Aug.) 1954.
- 208. Boggs, E. F.: Cortisone: contraindications and indications, J. Indiana M. A. 48: 869 (Aug.) 1955.
- Bohatirchuk, F.: The ageing vertebral column (macro- and historadiographical study), Brit. J. Radiol. 28: 389 (Aug.) 1955.
- Boisvert, P. L., Hilburg, L. E., and deForest, G. K.: A modification of the hemagglutination test in rheumatoid arthritis, Connecticut M. J. 19: 397 (May) 1955.
- Boland, E. W.: Experiences with 9-alpha-fluorohydrocortisone acetate in rheumatoid arthritis, Ann. New York Acad. Sc. 61: 591 (May 27) 1955.
- 212. Boland, E. W.: Oral hydrocortisone in the treatment of rheumatoid arthritis, M. Clin. North America 38: 337 (Mar.) 1954.
- Boland, E. W.: Oral hydrocortisone therapy in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 232 (Sept.) 1955.
- 214. Boland, E. W., and Headley, N. E.: Preliminary clinical trials with 9-alpha-fluoro-hydrocortisone acetate in rhuematoid arthritis, Ann. Rheumat. Dis. 13: 291 (Dec.) 1054
- 215. Boland, E. W.: Present status of hydrocortisone as a therapeutic agent in rheumatoid arthritis, Ann. New York Acad. Sc. 61: 349 (May 27) 1955.
- 216. Boland, E. W.: Recent advances in rheumatic diseases, California Med. 82: 65 (Feb.) 1955.

- Boldero, J. L., and Mitchell, G. P.: Osteochondritis of the superior tibial epiphysis,
 J. Bone and Joint Surg. 36B: 114 (Feb.) 1954.
- 218. Bollet, A. J., and Bunim, J. J.: The importance of serial joint x-rays in the evaluation of treatment of rheumatoid arthritis, M. Clin. North America 39: 439 (Mar.) 1955
- Bollet, A. J., Black, R., and Bunim, J. J.: Major undesirable side-effects resulting from prednisolone and prednisone, J. A. M. A. 158: 459 (June 11) 1955.
- Bollet, A. J., Boas, N. F., and Bunim, J. J.: Synthesis of hexosamine by connective tissue (in vitro), Science 120: 348 (Aug. 27) 1954.
- Bollet, A. J., and Bunim, J. J.: Treatment of systemic lupus erythematosus with prednisone and prednisolone, J. A. M. A. 159: 1501 (Dec. 17) 1955.
- Bolliger, A., and Gross, R.: Ammonia, urea and uric acid content of toenails in renal insufficiency and gout, Australian J. Exper. Biol. and M. Sc. 31: 385 (Aug.) 1953.
- Bolliger, A., and Gross, R.: Non-keratin uric acid determinations in gout, Australasian Ann. Med. 4: 208 (Aug.) 1955.
- 224. Bolton, R., and Barrie, H.: Acute renal failure after phenylbutazone, Brit. M. J. 1: 334 (Feb. 5) 1955.
- Bonnin, M., and Adey, W. R.: Investigations of muscular weakness in middle life: the so-called menopausal muscular dystrophy, Australasian Ann. Med. 3: 171 (Aug.) 1954.
- 226. Borkenhagen, R., and Elfenbaum, A.: Dentine dysplasia associated with rheumatoid arthritis and hypervitaminosis D, Oral Surg., Oral Med. and Oral Path. 8: 76 (Jan.) 1955.
- 227. Borman, A., Singer, F. M., and Numerof, P.: Growth-survival and sodium retaining activity of 9 a-halo derivatives of hydrocortisone, Proc. Soc. Exper. Biol. and Med. 86: 570 (Aug.-Sept.) 1954.
- 228. Bornstein, J., Silver, M., Neustadt, D. H., Berkowitz, S., and Steinbrocker, O.: Intraarticular hydrocortisone acetate in rheumatic diseases, Geriatrics 9: 205 (May) 1954.
- 229. Bossi, R.: Peritendinitis calcarea with multiple foci in the finger joints of a young subject, Brit. J. Radiol. 27: 692 (Dec.) 1954.
- 230. Boström, H., and Mansson, B., The action of salicylates and related compounds on the sulphate exchange of chondroitin sulphuric acid, J. Pharm. and Pharmacol. 7: 185 (Mar.) 1955.
- Boström, H., and Jorpes, E.: On the enzymatic exchange of the sulphate group of the animal sulpho-mucopolysaccharides, Experientia 10: 392 (Sept.) 1954.
- Boström, H., Rodén, L., and Vestermark, A.: Glutamine as an accelerator of chondroitin sulphate synthesis, Nature, London 176: 601 (Sept. 24) 1955.
- 233. Boström, H., Jorpes, E., Mansson, B., Roden, L., and Vestermark, A.: On the partial purification of a liver factor stimulating the sulphate exchange of chondroitin sulphuric acid, Ark. f. Kemi 8: 469, 1955.
- 234. Bosworth, D. M.: Bone and joint tuberculosis in childhood, Pediat. Clin. North America 2: 1129 (Nov.) 1955.
- 235. Bosworth, D. M., Fielding, J. W., Wilson, H., Guzman-Acosta, M., and Demarest, L. M.: A comparison of the efficacy of iproniazid (Marsilid) and isoniazid (Rimifon) in the treatment of bone and joint tuberculosis, Quart. Bull., Seaview Hosp. 15: 125 (Jan.) 1955.
- 236. Bosworth, D. M.: The role of the orbicular ligament in tennis elbow, J. Bone and Joint Surg. 37A: 527 (June) 1955.
- 237. Bosworth, D. M., Fielding, J. W., Demarest, L., and Bonaquist, M.: Spondylolisthesis, a critical review of a consecutive series of cases treated by arthrodesis, J. Bone and Joint Surg. 37A: 767 (July) 1955.

- 238. Boucek, R. J.: Biochemical and histologic aspects of in vivo cultivated connective tissue,—Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 155.
- Boucek, R. J., and Noble, N. L.: Connective tissue, a technique for its isolation and study, Arch. Path. 59: 553 (May) 1955.
- Bowes, J. H., Elliott, R. G., and Moss, J. A.: The composition of collagen and acidsoluble collagen of bovine skin, Biochem. J. 61: 143 (Sept.) 1955.
- Boyd, E. S., and Neuman, W. F.: Chondroitin sulfate synthesis and respiration in chick embryonic cartilage, Arch. Biochem. 51: 475 (Aug.) 1954.
- 242. Boyd, I. A.: The histological structure of the receptors in the knee-joint of the cat correlated with their physiological response, J. Physiol. 124: 476 (June) 1954.
- 243. Boyd, J. A., Patrick, S. I., and Reeves, R. J.: Roentgen changes observed in generalized scleroderma, Arch. Int. Med. 94: 248 (Aug.) 1954.
- 244. Boyes, J. H.: Dupuytren's contracture, notes on the age at onset and the relationship to handedness, Am. J. Surg. 88: 147 (July) 1954.
- 245. Boyle, A. C.: Pathology and incidence of spondylosis, Proc. Roy. Soc. Med. 47: 49 (Jan.) 1954.
- Boylston, B. F.: Basic orthopedic principles in rheumatoid arthritis, Texas State J. Med. 50: 616 (Aug.) 1954.
- 247. Bradford, F. K.: Intraspinal tumors: report of twelve cases, Dis. Nerv. System 15: 55 (Feb.) 1954.
- 248. Bragdon, D. E., and Dent, J. N.: Effect of cortisone and ACTH on renal fat and limb regeneration in adult salamanders, Proc. Soc. Exper. Biol. and Med. 87: 460 (Nov.) 1954.
- Brailsford, J. F.: Lesions of the intervertebral discs, Brit. J. Radiol. 28: 415 (Aug.) 1955.
- Brailsford, J. F.: The prevention, detection and treatment of osteoarthritis, Rheumatism 10: 2 (Jan.) 1954.
- 251. Brain, Sir R.: Cervical spondylosis, Ann. Int. Med. 41: 439 (Sept.) 1954.
- 252. Brain, Sir R.: Spondylosis: the known and the unknown, Ann. Rheumat. Dis. 13: 2 (Mar.) 1954.
- 253. Brashear, H. R.: The value of the intramedullary nail for knee fusion particularly for the Charcot joint, Am. J. Surg. 87: 63 (Jan.) 1954.
- 254. Braude, A. I.: Brucellosis: epidemiology and treatment, GP 11: 75 (Mar.) 1955.
- 255. Braunstein, H.: Periarteritis nodosa limited to the pulmonary circulation, Am. J. Path. 31: 837 (Sept.) 1955.
- 256. Brav, E. A.: An analysis of orthopedic causes of low back and sciatic pain, Am. J. Surg. 87: 235 (Feb.) 1954.
- 257. Brav, E. A., Hughes, C. W., and Macdonald, W. F.: The importance of proper early management of wounds of the extremities, Am. Acad. Orthop. Surgeons, Instructional Course Lecture 12: 44, 1955.
- 258. Breck, L. W., and Palafox, M.: Conservative treatment of lumbosacral backache: an outline of flexion management and an end-result study, Clin. Orthop. 5: 41, 1955.
- 259. Breese, B. B., and Disney, F. A.: The successful treatment of beta hemolytic strepto-coccal infections in children with a single injection of repository penicillin (Benzathine penicillin G), Pediatrics 15: 516 (May) 1955.
- Bridge, R. G., and Foley, F. E.: Placental transmission of the lupus erythematosus factor, Am. J. M. Sc. 227: 1 (Jan.) 1954.
- Brinsfield, D.: Current therapy of rheumatic fever in children, J. Am. M. Women's A. 10: 336 (Oct.) 1955.

- Broadbent, T. R.: Dupuytren's contracture, observations on the pathology, Rocky Mountain M. J. 52: 1087 (Dec.) 1955.
- Broadkin, H. A.: Cortisone in the rehabilitation of the arthritic patient, J. M. Soc. New Jersey 51: 411 (Oct.) 1954.
- 264. Broadman, J.: A new treatment for certain types of low back pain, Am. Pract. and Digest Treat. 6: 1193 (July) 1955.
- Broder, H. M.: The scope of lower extremity surgery in rehabilitation of the disabled rheumatoid, Pennsylvania M. J. 58: 1104 (Oct.) 1955.
- 266. Brodie, B. B., Yü, T. F., Burns, J. J., Chenkin, T., Paton, B. C., Steele, J. M., and Gutman, A. B.: Observations on G-25671, a phenylbutazone analogue (4-(phenylthioethyl)-1,2-diphenyl 3,5-pyrazolidine-dione), Proc. Soc. Exper. Biol. and Med. 86: 884 (Aug.) 1954.
- 267. Brodie, B. B., Lowman, E. W., Burns, J. J., Lee, P. R., Chenkin, T., Goldman, A., Weiner, M., and Steele, J. M.: Observations on the antirheumatic and physiologic effects of phenylbutazone (Butazolidin) and some comparisons with cortisone, Am. J. Med. 16: 181 (Feb.) 1954.
- Brodin, H.: Paths of nutrition in articular cartilage and intervertebral discs, Acta orthop. Scandinav. 24: 177, 1955.
- Bronsky, D., and Bernstein, A.: Acute gout secondary to multiple myeloma, a case report, Ann. Int. Med. 41: 820 (Oct.) 1954.
- 270. Brookes, R. B.: The physiotherapist and the injured shoulder, Physiotherapy 40: 113 (Apr.) 1954.
- Broomhead, R.: The management of surgical treatment of arthritis of the hip, Physiotherapy 41: 3 (Jan.) 1955.
- 272. Brown, D. B.: A case of spondylolisthesis in pregnancy, J. Obst. and Gynaec. Brit. Emp. 62: 603 (Aug.) 1955.
- Brown, J. R.: Radicular pain including the Guillain-Barre syndrome, Journal Lancet 75: 315 (July) 1955.
- 274. Brown, T., Nemiah, J. C., Barr, J. S., and Barry, H., Jr.: Psychologic factors in low-back pain, New England J. Med. 251: 123 (July 22) 1954.
- Brownell, K. D.: Community aspects of rheumatic fever, Bull. St. Francis Hosp. and Sanit. 11: 29 (Jan.) 1954.
- 276. Browning, J. S.: Some emotional factors in rheumatic disease, West Virginia M. J. 51: 103 (Apr.) 1955.
- 277. Bruck, E., Fearnley, M. E., Meanock, I., and Patley, H.: Phenylbutazone therapy: relation between the toxic and therapeutic effects and the blood level, Lancet 1: 225 (Jan. 30) 1954.
- 278. Bruckschwaiger, O.: An atypical form of De Quervain's disease, Canad. M. A. J. 71: 277 (Sept.) 1954.
- Brugsch, H. G., and Gowans, J. D. C.: Prolonged corticotropin therapy in rheumatoid arthritis, Geriatrics 9: 557 (Dec.) 1954.
- 280. Brusch, C. A., Keenan, G. F., Sargent, A. F., Dorgan, J. A., and Grasse, L. A.: Succinate-salicylate in treatment of arthritic disorders, Delaware State J. M. 26: 22 (Jan.) 1954.
- Brunson, J. G., and Davis, R. L.: Systemic fibrinoid diseases, similarity to experimental lesions in rabbits, Arch. Path. 60: 593 (Dec.) 1955.
- Bryson, K. D.: The treatment of chronic arthritis with a combination of cobra venom, formic acid, and silicic acid, Am. Surgeon 20: 751 (July) 1954.
- 283. Buchan, J. F.: Reiter's disease: a review of the present position, Proc. Roy. Soc. Med. 48: 432 (June) 1955.
- 284. Buchman, J.: Recent trends in the treatment of bone and joint tuberculosis, Bull. Hosp. Joint Dis. 15: 265 (Oct.) 1954.
- Buchman, J.: The therapy of pyogenic infections of bones and joints, J. Internat. Coll. Surgeons 24: 300 (Sept.) 1955.

- Buchman, J.: The use of oxytetracycline in infections of bones and joints and their soft-tissue coverings, Internat. Rec. Med. 168: 213 (Apr.) 1955.
- Buckler, W. St. J., and Bacon, G. E.: Haemarthrosis in Christmas disease, Ann. Phys. Med. 2: 212 (Apr.) 1955.
- Buckler, W. St. J.: Primary generalized osteoarthritis with involvement of the sterno-clavicular joints, Ann. Phys. Med. 2: 180 (Jan.) 1955.
- 289. Bunim, J. J., Ziff, M., and McEwen, C.: Cortisone therapy in rheumatoid arthritis: a four-year appraisal, Bull. Rheumat. Dis. 5: 73 (Sept.) 1954.
- Bunim, J. J., Ziff, M., and McEwen, C.: Evaluation of prolonged cortisone therapy in rheumatoid arthritis, Am. J. Med. 18: 27 (Jan.) 1955.
- 291. Bunim, J. J., Black, R. L., Bollet, A. J., and Pechet, M. M.: Metabolic effects of metacortandralone and metacortandracin, Ann. New York Acad. Sc. 61: 358 (May 27) 1955.
- Bunim, J. J.: Research activities in rheumatic diseases, Pub. Health Rep. 69: 437 (May) 1954.
- 293. Bunim, J. J., Sokoloff, L., Williams, R. R., and Black, R. L.: Rheumatoid arthritis: a review of recent advances in our knowledge concerning pathology, diagnosis. and treatment, J. Chron. Dis. 1: 168 (Feb.) 1955.
- 294. Bunim, J. J., Pechet, M. M., and Bollet, A. J.: Studies on metacortandralone and metacortandracin in rheumatoid arthritis, J. A. M. A. 157: 311 (Jan. 22) 1955.
- 295. Bunim, J. J., Editor: Transactions of Second National Conference on Research and Éducation in the Rheumatic Diseases, 1957, McGregor and Werner, Inc., Washington.
- Bunn, W. H., and Bennett, H. N.: Community control of rheumatic fever, J. A. M. A. 157: 986 (Mar. 19) 1955.
- 297. Bunnel, S.: Surgery of the rheumatic hand, J. Bone and Joint Surg. 37A: 759 (July) 1955.
- 298. Burke, J. B.: Erythema marginatum, Arch. Dis. Childhood 30: 359 (Aug.) 1955.
- 299. Burns, J. J., Rose, R. K., Goodwin, S., Reichenthal, J., Horning, E. C., and Brodie, B. B.: The metabolic fate of phenylbutazone (Butazolidin) in man, J. Pharmacol. and Exper. Therap. 113: 481 (Apr.) 1955.
- 300. Burns, J. J., Rose, R. K., Goodwin, S., Reichenthal, J., Horning, E., and Brodie, B. B.: Studies on the biotransformation of phenylbutazone (Butazolidin), Abstract, J. Pharmacol. and Exper. Therap. 113: 9 (Jan.) 1955.
- 301. Burt, H.: Discussion of hydrocortisone, Proc. Roy. Soc. Med. 48: 425 (June) 1955. 302. Burt, H. A., Fletcher, W. D., and Mattingly, S.: Pitfalls in the diagnosis of back-
- ache, Ann. Phys. Med. 2: 1 (Jan.) 1954.

 303. Burton, D., Hall, D. A., Keech, M. K., Reed, R., Saxl, H., Tunbridge, R. E., and Wood, M. I.: Apparent transformation of collagen fibrils into "elastin" Nature
- Wood, M. J.: Apparent transformation of collagen fibrils into "elastin," Nature 176: 966 (Nov. 19) 1955.

 304. Bushnell, L. F.: Postural backache of the gynecic patient, Clin. Orthop. 5: 164, 1955.
- 305. Busse, E. A.: Treatment of rheumatoid arthritis by a combination of cortisone and
- 305. Busse, E. A.: Treatment of rheumatoid arthritis by a combination of cortisone and salicylates, Clin. Med. 2: 1105 (Nov.) 1955.
- 306. Butler, J. J.: Scleroderma, GP 12: 103 (Sept.) 1955.
- Butler, K. R., and Palmer, J. A.: Cryoglobulinaemia in polyarteritis nodosa with gangrene of extremities, Canad. M. A. J. 72: 686 (May) 1955.
- Butson, A. R. C.: Intra-articular hydrocortisone in orthopaedic conditions, Canad. M. A. J. 70: 51 (Jan.) 1954.
- 309. Butterworth, R. D.: Synovectomy in treatment of tuberculosis of knee in children, South. M. J. 47: 582 (June) 1954.
- 310. Buxton, St. J. D.: Arthroplasty, Ann. Roy. Coll. Surgeons, England 14: 1 (Jan.) 1954.
- 311. Buzard, J. A., Bishop, C., and Talbott, J. H.: The conversion of uric acid to allantoin in the normal and gouty human, J. Biol. Chem. 211: 559 (Dec.) 1954.

- 312. Buzard, J. A., Bishop, C., and Talbott, J. H.: The fate of uric acid in the normal and gouty human being, J. Chron. Dis. 2: 42 (July) 1955.
- 313. Bywaters, E. G. L.: Heel lesions of rheumatoid arthritis, Ann. Rheumat. Dis. 13: 42 (Mar.) 1954.
- 314. Bywaters, E. G. L.: Treatment of rheumatic fever, Circulation 14: 1153 (Dec.) 1956.
- 315. Cahen, I.: Chondromalacia of the patella, J. Louisiana M. Soc. 107: 19 (Jan.) 1955.
- 316. Cairo, A. A.; Reiter's syndrome, Bull. Georgetown Univ. M. Center 8: 86 (Jan.) 1955.
- 317. Caldwell, I. W.: A dermatomyositic symptom-complex associated with malignant disease, Brit. J. Cancer 9: 575 (Dec.) 1955.
- 318. Calhoun, F. P., Jr.: Diseases of the uveal tract, Arch. Ophth. 51: 376 (Mar.) 1954.
- Calkins, E., Soodak, M., and Bauer, W.: Metabolism and clinical significance of the carbohydrate components of connective tissue, New England J. Med. 253: 865 (Nov. 17) 1955.
- 320. Calkins, E., and Bauer, W.: The protean manifestations of the connective tissue diseases, M. Clin. North America 39: 325 (Mar.) 1955.
- 321. Cambon, K. G., and Cambon, E. N.: Treatment of chronic gonorrhoea with long-acting penicillin, Canad. M. A. J. 72: 221 (Feb.) 1955.
- 322. Cameron, B. M., and McGehee, F. O.: Horseshoe-shaped Baker's cyst of the knee, J. Bone and Joint Surg. 37A: 863 (July) 1955.
- 323. Cameron, M. G. P.: Chronic tophaceous gout, Canad. M. A. J. 72: 205 (Feb. 1) 1955.
- Campbell, D. A.: Possible solution of the cardiac, epileptic and degenerative disease problem in industry, Indust. Med. 23: 451 (Oct.) 1954.
- Campbell, D. J., and Doyle, J. O.: Tabetic Charcot's spine, report of eight cases, Brit. M. J. 1: 1018 (May 1) 1954.
- Campbell, J. A., and Silver, R. A.: Roentgen manifestations of epidural granulomas of the spine with a report of ten cases, Am. J. Roentgenol. 72: 229 (Aug.) 1954.
- 327. Campbell, L. S., Hamsa, W. R., and Burney, D. W., Jr.: Lumbosacral strain, Nebraska M. J. 40: 237 (July) 1955.
- 328. Campos, O. P.: Bone and joint tuberculosis and its treatment, J. Bone and Joint Surg. 37A: 937 (Oct.) 1955.
- 329. Canadian Arthritis and Rheumatism Society, Toronto, Canada: Seventh annual report, 1955.
- 330. Canadian Arthritis and Rheumatism Society, Toronto, Canada: News letter, May and Nov., 1955.
- Canellakis, E. S., Tuttle, A. L., and Cohen, P. P.: A comparative study of the endproducts of uric acid oxidation by peroxidases, J. Biol. Chem. 213: 397 (Mar.) 1955.
- 332. Canellakis, E. S., and Cohen, P. P.: The end-products and intermediates of uric acid oxidation by uricase, J. Biol. Chem. 213: 385 (Mar.) 1955.
- 333. Canellakis, E. S., and Cohen, P. P.: On the nature of oxonic acid and allantoxaidin as oxidation products of uric acid and allantoin, J. Biol. Chem. 213: 379 (Mar.) 1955.
- 334. Canizares, O., Shatin, H., and Rosenbaum, H. M.: The present status of the use of corticotropin, cortisone, hydrocortisone, and prednisone in dermatology, New York State J. M. 55: 3583 (Dec. 15) 1955.
- 335. Caraway, W. T.: Determination of uric acid in serum by a carbonate method, Am. J. Clin. Path. 25: 840 (July) 1955.
- 336. Cardell, B. S., and Gurling, K. J.: Observations on the pathology of Sjögren's syndrome, J. Path. and Bact. 68: 137 (July) 1954.
- 337. Carlson, F. S.: The diagnostic significance of acute phase protein in synovial exudates, Acta Rheum. Scandinav. 1: 267, 1955.
- Carmichael, D. B.: The corrected Q-T duration in acute and convalescent rheumatic fever, Am. Heart J. 50: 528 (Oct.) 1955.

- 339. Carr, C. R., Berley, F. V., and Davis, W. C.: Pigmented villonodular synovitis of the hip joint, J. Bone and Joint Surg. 36A: 1007 (Oct.) 1954.
- Carr, C. R., and Dunn, A. W.: Surgical management of low back disability, U. S. Armed Forces M. J. 5: 1117 (Aug.) 1954.
- Carr, D. T., and Gage, R. P.: The geographic distribution of sarcoidosis, Am. Rev. Tuberc. 70: 899 (Nov.) 1954.
- 342. Carrera, A. E., Reid, M. V., and Kurnick, N. B.: Differences in susceptibility of polymorphonuclear leukocytes from several species to alteration by systemic lupus erythematosus serum: application to a more sensitive L. E. phenomenon test, Blood 9: 1165 (Dec.) 1954.
- 343. Carroll, R. E., and Garcia, A.: Acute calcium deposits in the hand, J. A. M. A. 157: 422 (Jan. 29) 1955.
- 344. Carroll, R. E., and Taber, T. H.: Digital arthroplasty of the proximal interphalangeal joint, J. Bone and Joint Surg. 36A: 912 (Oct.) 1954.
- Carter, J. R.: Ankylosing spondylitis and pulmonary tuberculosis, Brit. J. Tuberc.
 49: 293 (Oct.) 1955.
- 346. Cassels, D. E.: The diagnosis of rheumatic fever, Pediat. Clin. North America 1: 251 (Feb.) 1954.
- Casten, G. G., and Boucek, R. J.: Use of relaxin in the treatment of scleroderma, J. A. M. A. 166: 319 (Jan. 25) 1958.
- 348. Castor, C. W.: Production of mucopolysaccharides by synovial cells in a simplified tissue culture medium, Proc. Soc. Exper. Biol. and Med. 94: 51 (Jan.) 1957.
- Castro, F. G.: Relapsing febrile non-suppurative panniculitis (Weber-Christian syndrome), Philippine M. A. J. 31: 461 (Sept.) 1955.
- 350. Catanzaro, F. J., Brock, L., Chamovitz, R., Perry, W. D., Siegel, A. C., Stetson, C. A., Rammelkamp, C. H., Houser, H. B., Stolzer, B. L., Wannamaker, L. W., and Hahn, E. O.: Effect of oxytetracycline therapy of streptococcal sore throat on the incidence of acute rheumatic fever, Ann. Int. Med. 42: 345 (Feb.) 1955.
- 351. Catanzaro, F. J., Stetson, C. A., Morris, A. J., Chamovitz, R., Rammelkamp, C. H., Jr., Stolzer, B. L., and Perry, W. D.: The role of the streptococcus in the pathogenesis of rheumatic fever, Am. J. Med. 17: 749 (Dec.) 1954.
- 352. Catchpole, B. N., Jepson, R. P., and Kellgren, J. H.: Peripheral vascular effect of cortisone in rheumatoid arthritis, scleroderma, and other related conditions, Ann. Rheumat. Dis. 13: 302 (Dec.) 1954.
- 353. Cave, A. J. E., Griffiths, J. D., and Whiteley, M. M.: Osteo-arthritis deformans of the Luschka joints, Lancet 1: 176 (Jan. 22) 1955.
- Cecchi, E., and Ferraris, F.: Serum diphenylamine reaction in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 267 (Sept.) 1955.
- 355. Chakraborty, A. N., Banerjee, A. K., and Ghosh, S.: Ehler-Danlos syndrome (cutis hyperelastica), J. Indian M. A. 23: 344 (May) 1954.
- 356. Chamovitz, R., Catanzaro, F. J., Stetson, C. A., and Rammelkamp, C. H., Jr.: Prevention of rheumatic fever by treatment of previous streptococcal infections. I. Evaluation of benzathine penicillin G, New England J. Med. 251: 466 (Sept. 16) 1954.
- 357. Chance, J., Lotsof, E. J., Pine, I., Patterson, R. M., and Craig, J.: Effects of cortisone on psychiatric patients, Psychosom. Med. 16: 516 (Nov.-Dec.) 1954.
- 358. Chaney, W. C.: Treatment of chronic rheumatoid arthritis, J. Tennessee M. A. 47: 323 (Aug.) 1954.
- 359. Charnley, J.: Acute lumbago and sciatica, Brit. M. J. 1: 344 (Feb. 5) 1955.
- 360. Charron, K. C.: Medical rehabilitation in the development of health services in Canada, Canad. J. Pub. Health 46: 437 (Nov.) 1955.
- 361. Charteris, A. A.: The treatment of haemangioma and ankylosing spondylitis, Acta radiol. Supp. 116: 345, 1954.

- 362. Chatterjee, S. K.: Myositis ossificans progressiva, J. Indian M. A. 25: 561 (Dec. 16) 1955.
- 363. Cheshire, D. J. E., and Nichols, P. J. R.: The early stages of ankylosing spondylitis, Rheumatism 11: 79 (Oct.) 1955. .
- Childress, H. M.: Popliteal cysts associated with undiagnosed posterior lesions of the medial meniscus, J. Bone and Joint Surg. 36A: 1233 (Dec.) 1954.
- Chinn, A. B., and Mason, R.: Some experiences with physical disabilities from chronic illness in old persons, J. Chron. Dis. 2: 534 (Nov.) 1955.
- Christensen, E.: Peptic ulcer perforation after phenylbutazone, Brit. M. J. 2: 916
 (Oct. 16) 1954.
- Christensen, R. W.: Surgical correction of complete bilateral ankylosis of the mandible, Oral Surg., Oral Med. and Oral Path. 8: 1235 (Dec.) 1955.
- 368. Christie, A. B.: Arthritis in infectious diseases, Rheumatism 11: 68 (July) 1955.
- Christie, B. G. B.: Local hydrocortisone in De Quervain's disease, Brit. M. J. 1: 1501 (June 25) 1955.
- Christie, G. S.: Pulmonary lesions in rheumatoid arthritis, Australasian Ann. Med.
 49 (Feb.) 1954.
- Citron, K. M.: Sarcoidosis, hypercalcaemia, calcinosis, and renal impairment, Proc. Roy. Soc. Med. 47: 507 (July) 1954.
- 372. Clark, C. J. M.: Calcinosis circumscripta, Proc. Roy. Soc. Med. 48: 535 (July) 1955.
- 373. Clark, E. C., and Bailey, A. A.: Neurologic and psychiatric findings in lupus erythematosus, Tr. Am. Neurol. A. 79: 15, 1954.
- 374. Clark, I., and Umbreit, W. W.: Effect of cortisone and other steroids upon in vitro synthesis of chondroitin sulfate, Proc. Soc. Exper. Biol. and Med. 86: 558 (July) 1954
- Clark, R. M., and Anderson, W.: Rheumatic activity in auricular appendages removed at mitral valvoplasty, Am. J. Path. 31: 809 (Sept.-Oct.) 1955.
- 376. Clark, W. S., Watkins, A. L., Tonning, H. O., and Bauer, W.: The effects of resistance exercises on the nitrogen, phosphorus, and calcium metabolism of patients with rheumatoid arthritis, J. Clin. Investigation 33: 505 (Apr.) 1954.
- Clark, W. S.: Second interim session, American Rheumatism Association, Bull. Rheumat. Dis. 6: 103 (Feb.) 1956.
- 378. Clarke, E.: Cervical myelopathy, a common neurological disorder, Lancet 1: 171 (Jan. 22) 1955.
- 379. Clarke, E., and Little, J. H.: Cervical myelopathy, a contribution to its pathogenesis, Neurology 5: 861 (Dec.) 1955.
- 380. Cleveland, D. A.: Management of cervical disk and cervical arthritis syndromes, Postgrad. Med. 18: 99 (Aug.) 1955.
- 381. Cleveland, S. E., and Fisher, S.: Behavior and unconscious fantasies of patients with rheumatoid arthritis, Psychosom. Med. 16: 327 (July) 1954.
- Clifton, F., and Greer, C. H.: Ocular changes in acute systemic lupus erythematosus, Brit. J. Ophth. 39: 1 (Jan.) 1955.
- 383. Clinicopathologic conference: Cough, dyspnea, and chest pain, U. S. Armed Forces M. J. 6: 1349 (Sept.) 1955.
- 384, Clinicopathological conference: Gout, New England J. Med. 251: 621 (Oct. 7) 1954.
- 385. Clinton-Thomas, C. L., and Young, W. B.: Multiple pseudo-cystic tuberculosis of bone, J. Bone and Joint Surg. 37B: 624 (Nov.) 1955.
- 386. Clough, P. W.: Collagen diseases (editorial), Ann. Int. Med. 42: 209 (Jan.) 1955.
- Clough, P. W.: The value of steroids in the treatment of rheumatoid arthritis (editorial), Ann. Int. Med. 43: 1341 (Dec.) 1955.
- 388. Cloward, R. B.: Multiple ruptured lumbar discs, Ann. Surg. 142: 190 (Aug.) 1955.
- 389. Cloyd, W. L.: Bursitis of the hip, Mississippi Valley M. J. 76: 219 (Nov.) 1954.
- Cobb, S., Merchant, W. R., and Warren, J. E.: An epidemiologic look at the problem of classification in the field of arthritis, J. Chron. Dis. 2: 50 (July) 1955.

- Cobb, S., Warren, J., Thompson, D., and Ciocco, A.: The epidemiology of rheumatoid arthritis with particular reference to the importance of morning stiffness, Pennsylvania M. J. 57: 37 (Jan.) 1954.
- Cobey, M. C.: Low-back pain and its related conditions particularly the lumbar disc,
 J. Kentucky M. A. 53: 781 (Sept.) 1955.
- 393. Coburn, A. F., Graham, C. E., and Haninger, J.: The effect of egg yolk in diets on anaphylactic arthritis (passive Arthus' phenomenon) in the guinea pig, J. Exper. Med. 100: 425 (Nov.) 1954.
- 394. Coburn, A. F., and Haninger, J.: The serum diphenylamine (DPA) reaction in experimental arthritis, J. Exper. Med. 99: 1 (Jan.) 1954.
- Cochran, J. B.: Further observations on the metabolic stimulating effect of salicylate, Brit. M. J. 1: 733 (Mar. 27) 1954.
- Coggeshall, H. C.: Clinical evaluation and management of the painful joint, Texas State J. M. 50: 612 (Aug.) 1954.
- Cohen, A., Scott, G. E., Turner, R. F., and Rose, I.: Intra-articular and para-vertebral injection of cortisone in osteoarthritis of spine, J. A. M. A. 159: 1724 (Dec. 31) 1955.
- Cohen, A., Rose, I., and Seven, M. J.: Intra-articular injection of cortisone in the treatment of rheumatoid and hypertrophic arthritis, New England J. Med. 250: 507 (Mar. 25) 1954.
- Cohen, A., Turner, R., and Dunsmore, R.: Prednisone in the treatment of rheumatoid arthritis, New England J. Med. 253: 1150 (Dec. 29) 1955.
- Cohen, A. K.: Disseminated lupus erythematosus: a clinico-pathological review of seven cases, Australasian Ann. Med. 3: 64 (Feb.) 1954.
- 401. Cohen, A. M., and Sulman, F. G.: Continuous intravenous ACTH infusions in small doses as a physiologic approach to treatment, J. Clin. Endocrinol. 14: 440 (Apr.) 1954.
- 402. Cohen, A. S., and Calkins, E.: A controlled study of chloroquine as an antirheumatic agent, Ninth International Congress on Rheumatic Diseases, Toronto, June, 1957.
- Cohen, C.: Optical rotation and helical polypeptide chain configuration in collagen and gelatin, J. Biophys. and Biochem. Cytol. 1: 203 (May 25) 1955.
- 404. Cohen, H., Freedman, H. H., Kleinberg, W., and Barnard, R.: Enhancement of adrenocorticotrophic activity, Acta endocrinol. 18: 169, 1955.
- 405. Cohen, H. H.: Unusual bone regeneration in Pott's disease, Am. J. Surg. 88: 336 (Aug.) 1954.
- 406. Cohen, L. A.: Activity of knee joint proprioceptors recorded from the posterior articular nerve, Yale J. Biol. and Med. 28: 225 (Dec.) 1955.
- 407. Cohen, R.: Unusual coccidioidomycosis cases, Arch. Pediat. 72: 275 (Aug.) 1955.
- Cohn, I.: Untoward reactions from phenylbutazone, New York State J. Med. 54: 1369 (May 1) 1954.
- Coke, H.: Electrophoretic analysis of serum proteins in chronic rheumatic diseases, Rheumatism 11: 27 (Apr.) 1955.
- Collins, D. H.: Recent advances in the pathology of chronic arthritis and rheumatic disorders, Post-Grad. M. J. 31: 602 (Dec.) 1955.
- Collins, E. J., and Olson, K. J.: Inhibition of steroid-induced adrenal hypofunction, Proc. Soc. Exper. Biol. and Med. 87: 76 (Oct.) 1954.
- 412. Collins, S. D.: A review of illness from chronic disease and its variations with age, sex, and season, with some trends, J. Chron. Dis. 1: 412 (Apr.) 1955.
- 413. Collins, S. D., Trantham, K. S., and Lehmann, J. L.: Sickness experience in selected areas of the U. S., U. S. Pub. Health Service Monog. No. 25, 1955.
- Collins, V. P.: Bone involvement in cryptococcosis (torulosis), Am. J. Roentgenol.
 102 (Jan.) 1950.
- 415. Collis, W. R. F., and MacDonald, A. J.: The beta streptococcal theory of rheumatic fever in the modern treatment of the condition, Acta pædiat. Supp. 100: 228, 1954.

- Colonna, P. C.: Spondylolisthesis, analysis of two hundred one cases, J. A. M. A. 154: 398 (Jan. 30) 1954.
- Colsky, J., Wallace, S., and Banowitch, M. M.: Desacetylmethycolchicine in acute gouty arthritis, New England J. Med. 253: 730 (Oct. 27) 1955.
- Comens, P.: Experimental hydralazine disease and its similarity to disseminated lupus erythematosus, J. Lab. and Clin. Med. 46: 803 (Nov.) 1955.
- 419. Compere, E. L.: Osteoarthritis of the hip, J. Am. Geriatrics Soc. 2: 673 (Oct.) 1954.
- 420. Compere, E. L.: The treatment of osteoarthritis of the hip by means of the prosthetic type of arthroplasty, Clin. Orthop. 6: 54, 1955.
- Cone, R. B., Hannigan, C. A., and Teicher, R.: Erythema multiforme bullosum following phenylbutazone treatment for arthritis, Arch. Dermat. and Syph. 69: 674 (June) 1954.
- Conley, C. L.: The blood in systemic lupus erythematosus, Bull. Rheumat. Dis. 5: 87 (Apr.) 1955.
- 423. Conner, S. K.: Calcinosis and collagen diseases, Arizona Med. 12: 277 (July) 1955.
- 424. Constance, T. J.: Localised myositis ossificans, J. Path. and Bact. 68: 381 (Oct.) 1954.
- 425. Conway, E. J.: Intradermal procaine therapy, J. Irish M. A. 34: 73 (Mar.) 1954.
- 426. Conway, H.: Dupuytren's contracture, Am. J. Surg. 87: 101 (Jan.) 1954.
- 427. Cooke, A. M.: Osteoporosis, Lancet 1: 877 (Apr. 30) 1955; 1: 929 (May 7) 1955.
- Cope, C. L., Hurlock, B., and Sewell, C.: The distribution of adrenal cortical hormone in some body fluids, Clin. Sc. 14: 25 (Feb.) 1955.
- 429. Cope, C. L.: The pharmacology of cortisone and corticotrophin, Practitioner 175: 537 (Nov.) 1955.
- Cope, C. L., and Sewell, C. E.: The presence of natural hydrocortisone in synovial fluid, Ann. Rheumat. Dis. 14: 392 (Dec.) 1955.
- Copeland, W. A.: Bone changes in diabetes, Proc. Roy. Soc. Med. 47: 345 (May) 1954.
- Copeman, W. S. C.: The indications for cortisone and ACTH in rheumatoid arthritis, Proc. Roy. Soc. Med. 47: 325 (May) 1954.
- Copeman, W. S. C., Dodds, Sir C., Savage, O., Glyn, J. H., and Fearnley, M. E.: Management of rheumatoid arthritis with prolonged cortisone administration, Brit. M. J. 1: 1109 (May 15) 1954.
- 434. Copp, D. H.: The function of bone in calcium and phosphorus regulation,—Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 143.
- 435. Cosnett, J. E.: Acute disseminated lupus erythematosus, report of a case treated with ACTH and cortisone, South African M. J. 28: 129 (Feb. 13) 1954.
- Costello, M. J.: Cutaneous manifestations of systemic diseases, New York State J. Med. 55: 2014 (July) 1955.
- Court Brown, W. M., and Abbatt, J. D.: The incidence of leukaemia in ankylosing spondylitis treated with x-rays, Lancet 1: 1283 (June 25) 1955.
- 438. Coventry, M. B.: Diagnosis of shoulder pain, Wisconsin M. J. 53: 299 (May) 1954.
- Coventry, M. B.: The use of cortisone and hydrocortisone (compound F) in treatment of the painful shoulder, Proc. Staff Meet., Mayo Clin. 29: 58 (Jan. 27) 1954.
- 440. Coverdale, H.: Sjögren's syndrome as a constitutional defect, New Zealand M. J. 54: 641 (Dec.) 1955.
- 441. Cowan, P. M., McGavin, S., and North, A. C. T.: The polypeptide chain configuration of collagen, Nature, London 176: 1062 (Dec. 3) 1955.
- 442. Cowan, T. W.: Unusual ocular lesions in systemic lupus erythematosus, Postgrad. Med. 16: 561 (Dec.) 1954.
- Cowdell, R. H.: Sarcoidosis, with special reference to diagnosis and prognosis, Quart. J. Med. 23: 29 (Jan.) 1954.

- 444. Coyer, A. B.: Citrate iontophoresis in rheumatoid arthritis of the hands, Ann. Phys. Med. 2: 16 (Jan.) 1954.
- 445. Coyer, A. B., and Curwen, I. H. M.: Low back pain treated by manipulation, Brit. M. J. 1: 705 (Mar. 19) 1955.
- 446. Cozen, L.: Office care of chronic pain in the arm and hand, GP 12: 75 (Oct.) 1955.
- 447. Craig, R. M., Pugh, D. G., and Soule, E. H.: The roentgenologic manifestations of synovial sarcoma, Radiology 65: 837 (Dec.) 1955.
- 448. Craig, W. McK., and Witt, J. A.: Cervical disk, shoulder-arm-hand syndrome, Post-grad. Med. 17: 267 (Apr.) 1955.
- 449. Craigmyle, M. B. L.: Studies of cartilage autografts and homografts in the rabbit, Brit. J. Plast. Surg. 8: 93 (July) 1955.
- 450. Crain, D. C.: Omodynia-the painful shoulder, Am. J. Nursing 54: 579 (May) 1954.
- Crawford, Y. E., and Robinson, J. J.: Method for determining antistreptolysin O titer using capillary blood, Am. J. Clin. Path. 24: 1103 (Sept.) 1954.
- 452. Creger, W. P., and Houseworth, J. H.: Erythrophagocytosis and thrombocytopathy occurring during the course of a Henoch-Schönlein syndrome due to quinine, Am. J. Med. 17: 423 (Sept.) 1954.
- 453. Crisp, E. J.: Disc lesions, fact and fallacy, Guy's Hosp. Gaz. 69: 475 (Nov. 26) 1955.
- 454. Crisp, E. J., and Kendall, P. H.: Hydrocortisone in lesions of soft tissues, Lancet 1: 476 (Mar. 5) 1955.
- Crisp, E. J., and Kendall, P. H.: Treatment of periarthritis of the shoulder with hydrocortisone, Brit. M. J. 1: 1500 (June 25) 1955.
- 456. Crone, C., and Lassen, U. V.: The action of probenecid (p-[di-n-propylsulphamyl]-benzoic acid) on uric acid excretion and plasma uric acid level in normal human subjects, Acta pharmacol. et toxicol. 11: 295, 1955.
- 457. Crone, C., and Lassen, U. V.: The effect of salicylic acid and acetylsalicylic acid on uric acid excretion and plasma uric acid concentration in the normal human subject, Acta pharmacol. et toxicol. 11: 355, 1955.
- 458. Crone, C., and Lassen, U. V.: Mechanism of increased renal urate excretion during administration of salicylic acid, Acta pharmacol. et toxicol. 11: 362, 1955.
- 459. Crone, C., and Lassen, U. V.: The mechanism of the increased renal excretion of urate during the administration of probeneed, Acta pharmacol. et toxicol. 11: 301, 1955.
- 460. Cronheim, G., and Hyder, N.: Effect of salicylic acid on adrenal-pituitary system. III. Studies on mechanism of this effect, Proc. Soc. Exper. Biol. and Med. 86: 409 (July) 1954.
- Crosbie, S.: Treatment of a case of relapsing panniculitis with cortisone and ACTH, Ann. Int. Med. 43: 622 (Sept.) 1955.
- Cruickshank, B.: The arteritis of rheumatoid arthritis, Ann. Rheumat. Dis. 13: 136
 (June) 1954
- Cruickshank, B.: The pathology of degenerative joint disease, Medicine Illus. (London) 9: 429 (July) 1955.
- Cruickshank, B., Macleod, J. G., and Shearer, W. S.: Subarticular pseudocysts in rheumatoid arthritis, J. Fac. Radiol., London 5: 218 (Jan.) 1954.
- 465. Cuningham, J. A. K.: Penicillin reactions, New Zealand M. J. 54: 261 (June) 1955.
- Cunningham, R. C.: A contribution to the genetics of gargoylism, J. Neurol., Neurosurg. and Psychiat. 17: 191 (Aug.) 1954.
- 467. Curran, R. C., and Kennedy, J. S.: The distribution of the sulphated mucopoly-saccharides in the mouse, J. Path. and Bact. 70: 449 (Oct.) 1955.
- 468. Curran, R. C., and Kennedy, J. S.: Utilization of sulphation by fibroblasts in the quartz focus, Nature, London 175: 435 (Mar. 5) 1955.
- 469. Currie, J. P.: Research in the rheumatic diseases, J. Chron. Dis. 2: 597 (Nov.) 1955. 470. Curtain, C. C.: The nature of the protein in the hyaluronic complex of bovine synovial
 - fluid, Biochem. J. 61: 688 (Dec.) 1955.

- Curtis, R. M.: Capsulectomy of the interphalangeal joints of the fingers, J. Bone and Joint Surg. 36A: 1219 (Dec.) 1954.
- 472. Curtiss, P. H., Jr., Clark, W. S., and Herndon, C. H.: Vertebral fractures resulting from prolonged cortisone and corticotropin therapy, J. A. M. A. 156: 467 (Oct. 2) 1054
- 473. Cutler, M.: ACTH in Stevens-Johnson syndrome (erythema multiforme exudativum), Am. Pract. and Digest Treat. 5: 612 (Aug.) 1954.
- 474. Dacso, M. M., and Rusk, H. A.: The problem of chronically ill and custodial patients in public institutions, J. Chron. Dis. 2: 600 (Nov.) 1955.
- 475. DalCortivo, L., Patterson, M. B., and Umberger, C. J.: Chemical studies on synovial fluid relative to intra-articular injection of hydrocortisone acetate, J. Lab. and Clin. Med. 46: 720 (Nov.) 1955.
- 476. Dalgliesh, C. E., and Neuberger, A.: The mechanism for the conversions of uric acid into allantoin and glycine, J. Chem. Soc. London, Part 3, 3407, 1954.
- 477. Dameshek, W.: Hemotoxic reactions to drugs, Postgrad. Med. 16: 369 (Nov.) 1954.
- 478. Dammin, G. J., Nora, J. R., and Reardan, J. B.: Hydralazine reaction: case with LE cells antemortem and postmortem, and pulmonary, renal, splenic, and muscular lesions of disseminated lupus erythematosus, J. Lab. and Clin. Med. 46: 806 (Nov.) 1955.
- 479. Danielli, J. F.: Phosphatases and other enzymes considered in relation to active transport and the functions of fibrous protein structures, Proc. Roy. Soc. London, S. B 142: 146 (Mar.) 1954.
- Daniels, R. S., Gulotta, G. A., and Peterson, W. L.: The withdrawal effects of cortisone in the therapy of rheumatic fever in young adults, U. S. Armed Forces M. J. 5: 176 (Feb.) 1954.
- Darmady, E. M., Griffiths, W. J., Spencer, H., Mattingly, D., Stranak, F., and De Wardener, H. E.: Renal tubular failure associated with polyarteritis nodosa, Lancet 1: 378 (Feb. 19) 1955.
- Dauphinee, J. A., and Bruce-Robertson, A.: The plasma proteins in rheumatoid arthritis, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 31.
- Davidson, E. A., and Meyer, K.: Chondroitin, a new mucopolysaccharide, J. Biol. Chem. 211: 605 (Dec.) 1954.
- 484. Davies, D. V., and Young, L.: The distribution of radioactive sulphur (358) in the fibrous tissues, cartilages and bones of the rat following its administration in the form of inorganic sulphate, J. Anat. 88: 174 (Apr.) 1954.
- 485. Davies, H. R.: Phenylbutazone in arthritis, Ann. Phys. Med. 2: 8 (Jan.) 1954.
- 486. Davies, H. R.: Phenylbutazone in arthritis, Medicine Illus. (London) 8: 139 (Mar.) 1954.
- 487. Davis, A. R., Miller, G. V., and Smith, E. T.: Pellegrini-Stieda's disease, Texas State J. Med. 50: 608 (Aug.) 1954.
- Davis, H. R. L.: Root pain from cervical osteoarthritis simulating angina pectoris, Canad. M. A. J. 72: 520 (Apr. 1) 1955.
- Davis, J. S., Jr., and Bartfeld, H.: The effect of intravenous colchicine on acute gout, Am. J. Med. 16: 218 (Feb.) 1954.
- Dawson, I. M. P.: The histology and histochemistry of gargoylism, J. Path. and Bact. 67: 587 (Apr.) 1954.
- Dawson, J. J. Y.: Scleroderma with pulmonary involvement and chronic bronchitis, Proc. Roy. Soc. Med. 48: 152 (Mar.) 1955.
- 492. de Blecourt, J. J.: Rheumatism and social medicine in the Netherlands, Rheumatism 11: 83 (Oct.) 1955.
- 493. de Blecourt, J. J.: "Screening" of the population for rheumatic diseases, Ann. Rheumat. Dis. 13: 338 (Dec.) 1954.

- 494. DeGinder, W. L.: Osteochondritis dissecans of the talus, Radiology 65: 590 (Oct.) 1955.
- 495. De Gispert-Cruz, I., and Escarpenter, G. J.: Compressive and neuritic sciatica, Rheumatism 10: 35 (Apr.) 1954.
- Deiss, W. P., and Leon, A. S.: Mucopolysaccharides of heart valve mucoprotein, J. Biol. Chem. 215: 685 (Aug.) 1955.
- Delarue, N. C.: Rotator cuff tendonitis and bicipital tenosynovitis, Canad. M. A. J. 73: 201 (Aug. 1) 1955.
- 498. Demartini, F., Boots, R. H., Snyder, A. I., Sandson, J., and Ragan, C.: Comparative effects of prednisone and cortisone, J. A. M. A. 158: 1505 (Aug. 27) 1955.
- Denko, C. W., Ruml, D., and Bergenstal, D. M.: Clinical experience with phenylbutazone in 205 patients, Am. Pract. and Digest Treat. 6: 1865 (Dec.) 1955.
- Denko, C. W., and Bergenstal, D. M.: The effect of hypophysectomy and growth hormone on S⁸⁶ fixation in cartilage, Endocrinology 57: 76 (July) 1955.
- Denny, F. W., Jr.: The prophylaxis of streptococcal infections, Chap. 13 of Streptococcal infections, edited by M. McCarty, 1954, Columbia University Press, New York.
- Dent, C. E., and Philpot, G. R.: Xanthinuria an inborn error (or deviation) of metabolism, Lancet 1: 182 (Jan. 23) 1954.
- Denton, R. O., and Sherrill, J. D.: Sciatica syndrome due to endometriosis of sciatica nerve, South. M. J. 48: 1027 (Oct.) 1955.
- 504. DePalma, A. F., and Callery, G. E.: Bicipital tenosynovitis, Clin. Orthop. 3: 69, 1954.
- 505. DePalma, A. F.: Frozen shoulder, Delaware State M. J. 26: 95 (May) 1954.
- DePalma, A. F.: Lesions of the knee in childhood, Pediat. Clin. North America 2: 1035 (Nov.) 1955.
- 507. Devas, M. B.: Arthroplasty of the hip: a review of 110 cup and replacement athroplasties, J. Bone and Joint Surg. 36B: 561 (Nov.) 1954.
- Devas, M. B., and Thomson, A. D.: Malignant synovioma, Proc. Roy. Soc. Med. 48: 168 (Mar.) 1955.
- Devitt, J. E., Samuels, P. B., Pirozynski, W. J., and Webster, D. R.: Morphology of tissue mast cells, the frequency of artifacts and the influence of certain biologic agents, Am. J. Path. 30: 391 (Mar.-Apr.) 1954.
- De Wet, I. S.: Acute osteomyelitis and suppurative arthritis of infants, South African M. J. 28: 81 (Jan. 30) 1954.
- Deyerle, W. M., and May, V. R., Jr.: Low back pain and sciatica, Virginia M. Monthly 81: 312 (July) 1954.
- Deyerle, W. M., and May, V. R., Jr.: Sciatica—etiology and treatment, Clin. Orthop. 4: 166, 1954.
- 513. Diamond, M. T.: Thrombophlebitis associated with gout, New York State J. Med. 53: 3011 (Dec. 15) 1953.
- 514. Diehl, A. M., Hamilton, T. R., Keeling, I. C., and May, J. S.: Long-acting repository penicillin in prophylaxis of recurrent rheumatic fever, J. A. M. A. 155: 1466 (Aug. 21) 1954.
- 515. Di Ferrante, N.: Quantitative colorimetric assay of acid mucopolysaccharides, J. Biol. Chem. 209: 579 (Aug.) 1954.
- 516. Dillon, R. N., and Majnarich, J. J.: Rheumatoid arthritis, encouraging clinical results in its treatment with placental extract, M. Times, New York 82: 199 (Mar.) 1954.
- Dillon, R. N., and Majnarich, J. J.: Rheumatoid arthritis. I. Review of diagnosis and treatment, Northwest Med. 54: 29 (Jan.) 1955.
- Dillon, R. N., and Majnarich, J. J.: Rheumatoid arthritis. II. Specific therapy, Northwest Med. 54: 156 (Feb.) 1955.
- 519. Dimson, S. B.: The diagnosis and treatment of Still's disease, Rheumatism 10: 18 (Jan.) 1954.

- Dingle, J. H.: The clinical pattern of streptococcal infection in man, Chapter 9 of Streptococcal infections, edited by M. McCarty, 1954, Columbia University Press, New York.
- Dinken, H.: Medical aspects of physical treatment in geriatrics, J. Am. Geriatrics Soc.
 367 (June) 1954.
- Dittrich, R. J.: Disability of the knee due to referred pain and related phenomena, J. Am. Geriatrics Soc. 3: 800 (Oct.) 1955.
- Dittrich, R. J.: The latissimus dorsi syndrome, Ohio State M. J. 51: 973 (Oct.) 1955.
 Dittrich, R. J.: Local anesthesia in diagnosis and treatment of low back pain, Am. Pract. and Digest Treat. 6: 859 (June) 1955.
- 525. Dittrich, R. J.: Somatic pain and autonomic concomitants, Am. J. Surg. 87: 66 (Jan.) 1954.
- 526. Dixon, A. St. J.: Rheumatism, the American scene, Lancet 2: 281 (Aug. 7) 1954.
- 527. Dixon, A. St. J., Ramcharan, S., and Ropes, M. W.: Rheumatoid arthritis: dye retention studies and comparison of dye and radioactivity labelled red cell methods for measurement of blood volume, Ann. Rheumat. Dis. 14: 51 (Mar.) 1955.
- Dixon, H. B. F.: ACTH and the control of adrenal secretion, Proc. Roy. Soc. Med. 48: 903 (Nov.) 1955.
- 529. Dixon, T. F., Mulligan, L., Nassim, R., and Stevenson, F. H.: Myositis ossificans progressiva: report of a case in which A.C.T.H. and cortisone failed to prevent reossification after excision of ectopic bone, J. Bone and Joint Surg., 36B: 445 (Aug.) 1954.
- 530. Dodd, K.: Recent advances in diagnosis of rheumatic heart disease in children, Mississippi Doctor 33: 59 (Aug.) 1955.
- Doig, W. G.: Some unusual cases of tendo-vaginitis stenosans, Proc. Roy. Soc. Med. 48: 98 (Feb.) 1955.
- Donaldson, I. A., and Nassim, J. R.: The artificial menopause, with particular reference to the occurrence of spinal porosis, Brit. M. J. 1: 1228 (May 29) 1954.
- Donaldson, W. F.: Transient synovitis of the hip joint, Pediat. Clin. North America 2: 1073 (Nov.) 1955.
- Done, A. K., Ely, R. S., Olsen, L. J., and Kelley, V. C.: The in vivo half-life of exogenous hydrocortisone in patients with rheumatic fever, Metabolism 4: 416 (Sept.) 1955.
- Done, A. K., Ely, R. S., and Kelley, V. C.: Response of plasma 17-hydroxycorticosteroids to salicylate administration in normal human subjects, Metabolism 4: 129 (Mar.) 1955.
- Done, A. K., Ely, R. S., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids.
 III. Blood levels in salicylate intoxication, J. Pediat. 44: 153 (Feb.) 1954.
- Done, A. K., Ely, R. S., Raile, R. B., and Kelley, V. C.: Studies of 17-hydroxy-corticosteroids. XIII. Effects of salicylate intoxication in rheumatic and non-rheumatic subjects, J. Pediat. 47: 727 (Dec.) 1955.
- 538. Done, A. K., Ely, R. S., Ainger, L. E., Seely, J. R., and Kelley, V. C.: Therapy of acute rheumatic fever, Pediatrics 15: 522 (May) 1955.
- Donnelly, G. H., and Campbell, R. E.: Surgical aspects of periarteritis nodosa, Arch. Surg. 69: 533 (Oct.) 1954.
- 540. Dordick, J. R., and Gluck, E. J.: Preliminary clinical trial with prednisone (Meti-corten) in systemic lupus erythematosus, Arch. Dermat. and Syph. 72: 276 (Sept.) 1955.
- Dordick, J. R., and Gluck, E. J.: Preliminary clinical trials with prednisone (Meticorten) in rheumatic diseases, J. A. M. A. 158: 166 (May 21) 1955.
- Dorfman, A., Roseman, S., Moses, F. E., Ludowieg, J., and Mayeda, M.: The biosynthesis of hyaluronic acid by group A streptococcus. III. Origin of the N-acetylglucosamine moiety, J. Biol. Chem. 212: 583 (Feb.) 1955.

- Dorfman, A.: Metabolism of the mucopolysaccharides of connective tissue, Pharmacol. Rev. 7: 1 (Mar.) 1955.
- 544. Dorfman, A.: The role of hormones in treatment of rheumatic fever, Pediatrics 15: 605 (May) 1955.
- 545. Dorney, E. R., Fowler, N. O., and Mannix, E. P.: Unilateral clubbing of the fingers due to absence of the aortic arch, Am. J. Med. 18: 150 (Jan.) 1955.
- 546. Dornhorst, A. C., Pierce, J. W., and Whimster, I. W.: The oesophageal lesion in scleroderma, Lancet 1: 698 (Apr. 3) 1954.
- 547. Dorpat, T. L., and Holmes, T. H.: Mechanisms of skeletal muscle pain and fatigue, Arch. Neurol. and Psychiat. 74: 628 (Dec.) 1955.
- 548. Doub, H. P., Goodrich, B. E., and Gish, J. R.: The pulmonary aspects of polyarteritis (periarteritis) nodosa, Am. J. Roentgenol. 71: 785 (May) 1954.
- Dougherty, J., and Sherman, M. S.: A report of four proved cases of tuberculous bone or synovial infection treated with streptomycin, J. Bone and Joint Surg. 37A: 1223 (Dec.) 1955.
- 550. Dougherty, J. W., Reisch, M., and Lewis, G. M.: Lowered resistance to infection resulting from cortisone and corticotropin, New York State J. M. 54: 2964 (Nov. 1) 1954.
- Dougherty, T. F., and Schneebeli, G. L.: The use of steroids as anti-inflammatory agents, Ann. New York Acad. Sc. 61: 328 (May 27) 1955.
- 552. Dowling, G. B.: Lupus erythematosus, Practitioner 173: 140 (Aug.) 1954.
- 553. Dowling, G. B.: Scleroderma and dermatomyositis, Brit. J. Dermat. 67: 275 (Aug.) 1955.
- Downs, J. W., and Cooper, W. G., Jr.: Surgical complications resulting from ACTH and cortisone medication, Am. Surgeon 21: 141 (Feb.) 1955.
- Dresner, E.: Aetiology and pathogenesis of rheumatoid arthritis, Am. J. Med. 18: 74 (Jan.) 1955.
- Dresner, E., and Schubert, M.: The comparative susceptibility to collagenase and trypsin of collagen, soluble collagens and renal basement membrane, J. Histochem. and Cytochem. 3: 360 (Sept.) 1955.
- 557. Drew, J. F.: Some aspects of pain in chronic rheumatic disease, M. J. Australia 2: 701 (Oct. 30) 1954.
- 558. Drury, M. I.: Polyarteritis nodosa, Medicine Illus. (London) 8: 227 (Apr.) 1954.
- Dubois, E. L.: Effect of quinacrine (Atabrine) upon lupus erythematosus phenomenon, Arch. Dermat. and Syph. 71: 570 (May) 1955.
- Dubois, E. L.: Nitrogen mustard in treatment of systemic lupus erythematosus, Arch. Int. Med. 93: 667 (May) 1954.
- Dubois, E. L.: Quinacrine (Atabrine) in treatment of systemic and discoid lupus erythematosus, Arch. Int. Med. 94: 131 (July) 1954.
- Dubois, E. L.: Systemic lupus erythematosus: early cytologic diagnosis, California Med. 80: 154 (Mar.) 1954.
- Duff, I. F., Robinson, W. D., Mikkelsen, W. M., and Chatelin, N. H.: Intra-articular hydrocortisone in rheumatoid arthritis, M. Clin. North America 39: 413 (Mar.) 1955.
- 564. Duff, I. F., Robinson, W. D., Mikkelsen, W. M., and Hemerline, A. M.: Metabolism of compound S in rheumatoid arthritis: effect on 17-ketosteroid excretion, J. Lab. and Clin. Med. 44: 790 (Nov.) 1954.
- 565. Dulin, W. E.: Anti-inflammatory activity of Δ'-9_a-fluorohydrocortisone acetate, Proc. Soc. Exper. Biol. and Med. 90: 115 (Oct.) 1955.
- Duncan, G. A., Hollins, G. G., Jr., and Thiemeyer, J. S., Jr.: Further experiences with the femoral head prosthesis in fractures and arthritis of the hips, Virginia M. Monthly 82: 349 (Aug.) 1955.
- 567. Dunlop, E.: Towards the conquest of arthritis, Canad. Hosp. 31: 47 (Sept.) 1954.

- 568. Durman, D. C.: Arthritis and injury, J. Michigan M. Soc. 54: 301 (Mar.) 1955.
- Dussik, K. T.: The ultrasonic field as a medical tool, Am. J. Phys. Med. 33: 5 (Feb.) 1954.
- Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Rheumatic and febrile syndrome during prolonged hydralazine treatment, J. A. M. A. 154: 23 (Jan. 2) 1954.
- Duthie, J. J. R.: Indications for ACTH and cortisone in rheumatoid arthritis, Proc. Roy. Soc. Med. 47: 323 (May) 1954.
- Duthie, J. J. R., Thompson, M., Weir, M. M., and Fletcher, W. B.: Medical and social aspects of the treatment of rheumatoid arthritis, Ann. Rheumat. Dis. 14: 133 (June) 1955.
- Duthie, J. J. R.: Rheumatism, collagen and cortisone, Practitioner 173: 125 (Aug.) 1954.
- 574. Duthie, J. J. R.: Rheumatoid arthritis, Post-Grad. M. J. 31: 609 (Dec.) 1955.
- 575. Duthie, J. J. R.: The value of long-term conservative treatment in rheumatoid arthritis, Bull. Rheumat. Dis. 4: 54 (May) 1954.
- Duthie, R. B., and Barker, A. N.: An autoradiographic study of mucopolysaccharide and phosphate complexes in bone growth and repair, J. Bone and Joint Surg. 37B: 304 (May) 1955.
- 577. Dwan, P. F.: Prophylaxis of rheumatic fever, Minnesota Med. 38: 702 (Oct.) 1955.
- Eadie, S., and Thompson, M.: Kerato-conjunctivitis sicca treated with cortisone and ACTH, Brit. J. Ophth. 39: 90 (Feb.) 1955.
- Eastham, R. D.: The erythrocyte sedimentation rate and the plasma viscosity, J. Clin. Path. 7: 164 (May) 1954.
- Eastoe, J. E.: The amino acid composition of mammalian collagen and gelatin, Biochem. J. 61: 589 (Dec.) 1955.
- Eaton, L. M.: The perspective of neurology in regard to polymyositis, a study of 41 cases, Neurology 4: 245 (Apr.) 1954.
- 582. Ebaugh, F. G., Jr., Peterson, R. E., Rodnan, G. P., and Bunim, J. J.: The anemia of arthritis, Bull. Rheumat. Dis. 5: 89 (May) 1955.
- Ebaugh, F. G., Jr., Peterson, R. E., Rodnan, G. P., and Bunim, J. J.: The anemia of rheumatoid arthritis. M. Clin. North America 39: 489 (Mar.) 1955.
- 584. Editorial: Adrenal cortical function in rheumatoid arthritis, South. M. J. 47: 518 (May) 1954.
- 585. Editorial: Ankylosing spondylitis, Brit. M. J. 2: 776 (Sept. 24) 1955.
- 586. Editorial: Cervical spine and nervous system, Lancet 1: 187 (Jan. 22) 1955.
- 587. Editorial: Clubbing of fingers, Brit. M. J. 1: 778 (Mar. 26) 1955.
- 588. Editorial: Cortisone and aspirin in rheumatoid arthritis, South. M. J. 47: 1121 (Nov.) 1954.
- Editorial: Cortisone and salicylates in rheumatic fever, M. J. Australia 1: 80 (Jan. 15) 1955.
- 590. Editorial: Cortisone in the balance, Rheumatism 10: 75 (Oct.) 1954.
- 591. Editorial: The Costen syndrome, M. J. Australia 2: 636 (Oct. 15) 1955.
- Editorial: Emotional factors in rheumatoid arthritis, South. M. J. 47: 795 (Aug.) 1954.
- 593. Editorial: Hormonal etiology of peptic ulcer, South. M. J. 47: 280 (Mar.) 1954.
- 594. Editorial: Hormones in the treatment of acute rheumatic fever, New England J. Med. 253: 478 (Sept. 15) 1955.
- 595. Editorial: Management of chronic gout, Lancet 2: 381 (Aug. 20) 1955.
- 596. Editorial: Myopathy and myositis, Lancet 1: 602 (Mar. 19) 1955.
- 597. Editorial: Prevention of rheumatic fever, J. A. M. A. 157: 1313 (Apr. 9) 1955.
- 598. Editorial: Prophylaxis in streptococcal epidemics, Lancet 1: 553 (Mar. 12) 1955.
- 599. Editorial: Rheumatism in New Zealand, New Zealand M. J. 54: 633 (Dec.) 1955.

- 600. Editorial: The treatment of arthritis and rheumatism in British Columbia, Physiotherapy 40: 208 (July) 1954.
- 601. Editorial: Use of cortisone in rheumatic carditis with congestive heart failure, J. A. M. A. 159: 196 (Sept. 17) 1955.
- 602. Edlund, T., and Juhlin, L.: Studies on the permeability of connective tissue. I. The effects of Dibenamine on the decreased dermal spread caused by intra-articular burns, corticotropine, posterior pituitary extract, adrenaline and noradrenaline, Acta pharmacol. et toxicol. 10: 390, 1954.
- 603. Edlund, T., and Juhlin, L.: Studies on the permeability of connective tissue. II. The effect of antihistamines, antiadrenergic agents, hexamethonium and some theophylline derivatives on dermal spread, Acta pharmacol. et toxicol. 11: 37, 1955.
- 604. Edlund, T., Juhlin, L., and Palis, A.: Studies on the permeability of connective tissue. III. The effects of desoxycorticosterone and cortisone on the resistance to flow of synovial membranes, Acta pharmacol. et toxicol. 11: 111, 1955.
- 605. Edlund, T., Juhlin, L., and Palis, A.: Studies on the permeability of connective tissue. IV. The effect of alloxan on the flow of fluid through normal and injured synovial membranes, Acta pharmacol. et toxicol. 11: 187, 1955.
- 606. Edström, G., and Gedda, P. O.: Investigation on the localisations and forms of some visceral anatomical lesions in rheumatic fever, Acta med. Scandinav. 147: 367, 1954.
- Edström, G.: Rheumatic fever, its symptoms, prevention and treatment, Acta Rheum. Scandinav. 1: 145, 1955.
- 608. Edward, D. G.: The pleuropneumonia group of organisms: a review, together with some new observations, J. Gen. Microbiol. 10: 27 (Feb.) 1954.
- 609. Edwards, J. E., Parkin, T. W., and Burchell, H. B.: Recurrent hemoptysis and necrotizing pulmonary alveolitis in a patient with acute glomerulonephritis and periarthritis nodosa, Proc. Staff Meet., Mayo Clin. 29: 193 (Apr. 7) 1954.
- 610. Egelius, N., Göhle, O., Jonsson, E., and Wahlgren, F.: Cardiac changes in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 11 (Mar.) 1955.
- 611. Ehrlich, J. C., and Greenberg, D.: Sicca syndrome, Gougerot-Sjögren disease, Arch. Int. Med. 93: 731 (May) 1954.
- 612. Eik-Nes, K., Sandberg, A. A., Tyler, F. H., and Samuels, L. T.: Plasma levels of 17-hydroxycorticosteroids following the administration of adrenal steroids, Acta endocrinol. 18: 244, 1955.
- 613. Eisen, D., Shapiro, I., and Fischer, J. B.: A case of cryptococcosis with involvement of lungs and spine, Canad. M. A. J. 72: 33 (Jan.) 1955.
- 614. Eisenstadt, H. B., and Eggers, G. W. N.: Arthritis mutilans (Doigt, Main, Pied en Lorgnette), J. Bone and Joint Surg. 37A: 337 (Apr.) 1955.
- 615. Eisenstadt, W. S., and Cohen, E. B.: Osteoporosis and compression fractures from prolonged cortisone and corticotropin therapy, Ann. Allergy 13: 252 (May-June) 1955.
- 616. Ekholm, R.: Nutrition of articular cartilage, Acta anat. 24: 329, 1955.
- 617. Ellery, R. S.: Gold, M. J. Australia 2: 762 (Nov. 6) 1954.
- 618. Elliot, A.: Advanced vitamin D resistant osteomalacia with Looser-Milkman's syndrome, Acta med. Scandinav. 152: 195, 1955.
- 619. Ellis, F. A., and Bundick, W. R.: Histology of lupus erythematosus, Arch. Dermat. and Syph. 70: 311 (Sept.) 1954.
- 620. Ellman, P., and Cudkowicz, L.: Pulmonary manifestations in the diffuse collagen diseases, Thorax 9: 46 (Mar.) 1954.
- 621. Ellman, P., Cudkowicz, L., and Elwood, J. S.: Therapy of "Felty's" syndrome, Ann. Rheumat. Dis. 14: 84 (Mar.) 1955.
- 622. Ellman, P., Cudkowicz, L., and Elwood, J. S.: Widespread serous membrane involvement by rheumatoid nodules, J. Clin. Path. 7: 239 (Aug.) 1954.

- 623. Elster, S. K., Wood, H. F., and Seely, R. D.: Clinical and laboratory manifestations of the postcommissurotomy syndrome, Am. J. Med. 17: 826 (Dec.) 1954.
- 624. Elster, S. K., and Wood, H. F.: Studies of C-reactive protein in patients with rheumatic heart disease. I. Lack of correlation between C-reactive protein and Aschoff bodies in left auricular appendage biopsies, Am. Heart J. 50: 706 (Nov.) 1955.
- 625. Elwood, J. S.: Polyarteritis nodosa in the lung of a newborn infant, Arch. Path. 60: 179 (Aug.) 1955.
- Ely, R. S.: The evaluation of pituitary adrenal cortical function, Essays on Pediatrics, 1955, p. 86.
- 627. Ely, R. S., Raile, R. B., Bray, P. F., and Kelley, V. C.: Studies of 17-hydroxy-corticosteroids. IV. Evaluation of a standard ACTH-17-hydroxycorticosteroid response test in children, Pediatrics 13: 403 (May) 1954.
- 628. Ely, R. S., Bray, P. F., Raile, R. B., and Kelley, V. C.: Studies of 17-hydroxy-corticosteroids. V. Responses of 17-hydroxycorticosteroids, eosinophils, and glucose to ACTH and epinephrine, J. Clin. Investigation 33: 1587 (Dec.) 1954.
- 629. Ely, R. S., Ainger, L. E., Seely, J. R., Done, A. K., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. X. Urinary excretion of 17-hydroxycorticosteroids in patients with rheumatic fever, J. Clin. Endocrinol. 15: 523 (May) 1955.
- 630. Ely, R. S., Done, A. K., Seely, J. R., Ainger, L. E., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. XI. Relation of plasma concentrations to urinary excretion in patients treated for rheumatic fever, J. Pediat. 47: 576 (Nov.) 1955.
- Emanuel, R. W.: Gargoylism with cardiovascular involvement in two brothers, Brit. Heart J. 16: 417 (Oct.) '1954.
- 632. Empire Rheumatism Council: Multi-centre controlled trial comparing cortisone acetate and acetyl salicylic acid in the long-term treatment of rheumatoid arthritis, results up to one year, Ann. Rheumat. Dis. 14: 353 (Dec.) 1955.
- 633. Engel, L. L., Carter, P., and Fielding, L. L.: Urinary metabolites of administered corticosterone. I. Steroids liberated by glucuronidase hydrolysis, J. Biol. Chem. 213: 99 (Mar.) 1955.
- 634. Engfeldt, B., and Hjertquist, S. O.: Biophysical studies on bone tissue. XV. A histo-chemical and microradiographic study on normal bone tissue, Acta path. et microbiol. Scandinav. 36: 385, 1955.
- 635. Engfeldt, B., Romanus, R., and Yden, S.: Histological studies of pelvospondylitis ossificans (ankylosing spondylitis) correlated with clinical and radiological findings, Ann. Rheumat. Dis. 13: 219 (Sept.) 1954.
- Engleman, E. P.: The annual meeting of the American Rheumatism Association, Bull. Rheumat. Dis. 6: 91 (Sept.) 1955.
- 637. Engleman, E. P., Krupp, M. A., Rinehart, J. F., Jones, R. C., and Gibson, J. R.: Hepatitis following the ingestion of phenylbutazone, J. A. M. A. 156: 98 (Sept. 11) 1954
- 638. Engleman, E. P., Krupp, M. A., Saunders, W. W., Wilson, L. E., and Fredell, E. W.: Rheumatoid arthritis, an evaluation of long-term treatment with cortisone, California Med. 80: 369 (May) 1954.
- 639. Engleman, E. P.: Treatment of the arthritides, a panel discussion, California Med. 82: 367 (May) 1955.
- 640. Ensign, D. C., and Sigler, J. W.: Osteoarthritis and rheumatoid arthritis, GP 11: 62 (Jan.) 1955.
- 641. Epstein, J. A., and Malis, L. I.: Compression of spinal cord and cauda equina in achondroplastic dwarfs, Neurology 5: 875 (Dec.) 1955.
- 642. Epstein, J. A.: The syndrome of herniation of the lower thoracic intervertebral discs with nerve root and spinal cord compression, J. Neurosurg. 11: 525 (Nov.) 1954.
- 643. Erickson, D. J.: Physical therapy for painful shoulders, Minnesota Med. 38: 556 (Aug.) 1955.

- 644. Esbenshade, J. H.: Continuous prophylaxis of streptococcal infection with oral benzathine penicillin G in rheumatic and congenital heart disease, Pennsylvania M. J. 58: 475 (May) 1955.
- 645. Estes, H. R., and Millikan, C. H.: Polyneuritis and radiculitis associated with multiple myeloma: report of case, Proc. Staff Meet., Mayo Clin. 29: 453 (Aug. 11) 1954.
- 646. Evans, J. A., and Eisenbeis, C. H., Jr.: 1-hydrazinophthalazine (Apresoline) toxicity: report of a case of arthritis of the rheumatoid type and pancytopenia, Lahey Clin. Bull. 9: 109 (Apr.) 1955.
- 647. Evans, J. A., and Steinberg, I.: Pulmonary complications of ACTH and cortisone: roentgen observations, Radiology 63: 515 (Oct.) 1954.
- 648. Evans, M., and Parker, R. A.: Honeycomb lung and mitral stenosis in scleroderma, Thorax 9: 154 (June) 1954.
- 649. Eversole, S. L., Jr.: Cases of disseminated lupus erythematosus diagnosed as idiopathic thrombocytopaenic purpura, Bull. Johns Hopkins Hosp. 96: 210 (May) 1955.
- 650. Faber, V., and Rosendal, K.: Streptococcal hyaluronidase. II. Studies on the production of hyaluronidase and hyaluronic acid by representatives of all types of hemolytic streptococci belonging to group A, Acta path. et microbiol. Scandinav. 35: 159, 1954.
- 651. Faber, V., and Rosendal, K.: Streptococcal-hyaluronidase. IV. The effect of penicillin on the production of hyaluronic acid and hyaluronidase by hemolytic streptococci (type 4, group A), Acta path. et microbiol. Scandinav. 37: 286, 1955.
- 652. Fahey, J. J., and Bollinger, J. A.: Trigger-finger in adults and children, J. Bone and Joint Surg. 36A: 1200 (Dec.) 1954.
- 653. Fahey, J. L., Leonard, E., Churg, J., and Godman, G.: Wegener's granulomatosis, Am. J. Med. 17: 168 (Aug.) 1954.
- 654. Farkas, K., and Podhragyay, L.: Changes in the structure of the adrenal cortex in socalled collagen diseases, Acta Morphol. Hung. 4: 132, 1954.
- 655. Farrell, G. L., and Laqueur, G.: Reduction of pituitary content of ACTH by cortisone, Endocrinology 56: 471 (Apr.) 1955.
- 656. Fassbender, H. G.: The incidence of rheumatic endocarditis, Am. Heart J. 50: 537 (Oct.) 1955.
- 657. Fawcitt, J.: The radiological pattern of pseudocoxalgia, Brit. J. Radiol. 27: 504 (Sept.) 1954.
- 658. Fawns, H. T., and Landells, J. W.: Histochemical studies of rheumatic conditions. II. The nodule of rheumatoid arthritis, Ann. Rheumat. Dis. 13: 28 (Mar.) 1954.
- 659. Fearnley, G. R., and Lackner, R.: Amyloidosis in rheumatoid arthritis, and significance of "unexplained" albuminuria, Brit. M. J. 1: 1129 (May 7) 1955.
- 660. Fearnley, G. R., Pirkis, J., De Coek, N., Lackner, R., and Meanock, R. I.: Diphenylamine reaction in rhuematoid arthritis, Ann. Rheumat. Dis. 14: 226 (Sept.) 1955.
- Feichtmeir, T. V., and Wrenn, H. T.: Direct determination of uric acid using uricase.
 Am. J. Clin. Path. 25: 833 (July) 1955.
- 662. Feinblatt, H. M.: Relief of muscular pains and spasms in muscular rheumatism, M. Times, New York 83: 700 (July) 1955.
- 663. Feinblatt, T. M., and Ferguson, E. A., Jr.: Sodium cinnamate as a salicylate additive for control of pain in arthritis and rheumatism, New York State J. Med. 55: 1891 (July 1) 1955.
- 664. Feinstein, B., Langton, J. N. K., Jameson, R. M., and Schiller, F.: Experiments on pain referred from deep somatic tissues, J. Bone and Joint Surg. 36A: 981 (Oct.) 1954.
- 665. Feldman, L., Cohnen, F., and Hirsch, H.: Fatal thrombocytopenic purpura following phenylbutazone (Butazolidin) therapy, Illinois M. J. 105: 83 (Feb.) 1954.
- 666. Fell, E. H., and Helman, R. T.: Reactivation of rheumatic fever following mitral commissurotomy, Arch. Surg. 71: 512 (Oct.) 1955.

- 667. Felländer, M.: Radical operation in tuberculosis of the spine, Acta orthop. Scandinav. Supp. 19, 1955.
- 668. Felts, W. R., Jr.: Hyperuricemia, Am. Pract. and Digest Treat. 6: 721 (May) 1955.
- 669. Fentress, V., and Campbell, R.: Splenectomy in Felty's syndrome: case report. Harper Hosp. Bull. 12: 31 (Jan.) 1954.
- Ferciot, C. F.: Recognition and management of degenerative joint diseases, Geriatrics
 121 (Mar.) 1954.
- 671. Ferguson, A. B., Jr.: Dorsal wedging round back in preadolescents, Pediat. Clin. North America 2: 951 (Nov.) 1955.
- 672. Ferguson, A. B., Jr.: Synovitis of the hip and Legg-Perthes disease, Clin. Orthop. 4: 180, 1954.
- 673. Fessler, J. H., Ogston, A. G., and Stanier, J. E.: Some properties of human and other synovial fluids, Biochem. J. 58: 656 (Dec.) 1954.
- 674. Ficarra, B. J.: Pannicular lumbosacroiliac hernia, Arch. Surg. 70: 229 (Feb.) 1955.
- 675. Fife, R., and Murdoch, W. R.: Observations on the electrocardiographic changes in acute rheumatism, Glasgow M. J. 36: 379 (Nov.) 1955.
- Finck, P. A.: Cortisone overdosage in rheumatoid arthritis, Arch. Path. 60: 374 (Oct.) 1955.
- 677. Findlay, G. H.: On elastase and the elastic dystrophies of the skin, Brit. J. Dermat. 66: 16 (Jan.) 1954.
- 678. Fineberg, S. K., and Altschul, A.: Nephropathy of gout, Ann. Int. Med. 44: 1182 (June) 1956.
- 679. Finestone, A. W.: Sarcoidosis, an analysis of twenty-one proved cases, Am. J. Roentgenol. 74: 455 (Sept.) 1955.
- Finlay, J. M., and MacDonald, R. I.: Acromegaly, Canad. M. A. J. 71: 345 (Oct.) 1954.
- 681. Finzi, N. S.: Treatment of arthritic limb-joints by x-ray therapy to the cervical or lumbar regions, Rheumatism 11: 86 (Oct.) 1955.
- 682. Fischer, F., and Lund, E.: The blood coagulation mechanism with especial reference to the prothrombin-proconvertin contents of plasma during long-term ACTH or cortisone therapy, Acta med. Scandinav. 149: 179, 1954.
- 683. Fischer, F.: Corticotropin and cortisone in rheumatoid arthritis, Acta med. Scandinav. Supp. 305, 1955.
- 684. Fischer, F., and Hastrup, B.: Cortisone and calcium balance (effect of calcium, vitamin-D and methylandrostenediol), Acta endocrinol. 16: 141, 1954.
- 685. Fischer, F., Harvald, B., and Brøchner-Mortensen, K.: Prolonged treatment of rheumatoid arthritis with cortisone, Danish M. Bull. 1: 18 (Mar.) 1954.
- 686. Fishbein, M.: The social aspects of rheumatic fever, Pediatrics 15: 610 (May) 1955.
- 687. Fisher, M.: Median neuropathy in the carpal tunnel, Canad. M. A. J. 71: 121 (Aug.) 1954.
- 688. Fisher, R. G., and Williams, J.: Ochronosis associated with degeneration of an intervertebral disc, J. Neurosurg. 12: 403 (July) 1955.
- 689. Fitzpatrick, T. J., and Woodruff, L. F.: Felty's syndrome, response to splenectomy after cortisone failure, Arch. Int. Med. 95: 333 (Feb.) 1955.
- 690. Fleming, J. W.: The Ehlers-Danlos syndrome: report of a case, J. Florida M. A. 42: 290 (Oct.) 1955.
- 691. Fleminger, J. J.: The differential effect of cortisone and of ACTH on mood, J. Ment. Sc. 101: 123 (Jan.) 1955.
- 692. Fletcher, E., Jacobs, J. H., and Rose, F. C.: The effect of periarticular procaine infiltration on joint temperature, Ann. Phys. Med. 2: 123 (Oct.) 1954.
- 693. Fletcher, E., and Rose, F. C.: Psoriasis spondylitica, Lancet 1: 695 (Apr. 2) 1955.
- 694. Fletcher, E., and Jacobs, J. H.: Psychogenic rheumatism, Proc. Roy. Soc. Med. 48: 66 (Feb.) 1955.

- Fletcher, E., Jacobs, J. H., and Markham, R. L.: Viscosity studies on hyaluronic acid of synovial fluid in rheumatoid arthritis and osteoarthritis, Clin. Sc. 14: 653 (Nov.) 1955.
- 696. Follis, R. H., Jr.: Osteoporosis, Bull. Rheumat. Dis. 4: 52 (Apr.) 1954.
- 697. Follis, R. H., Jr., Bush, J. A., Cartwright, G. E., and Wintrobe, M. M.: Studies on copper metabolism. XVIII. Skeletal changes associated with copper deficiency in swine, Bull. Johns Hopkins Hosp. 97: 405 (Dec.) 1955.
- 698. Forbes, J. C., Board, J. A., and Duncan, G. M.: Adrenal response of rats to salicylamide and sodium salicylate with and without para-aminobenzoic acid, Proc. Soc. Exper. Biol. and Med. 85: 37 (Jan.) 1954.
- Ford, D. K.: Natural history of arthritis following venereal urethritis, Ann. Rheumat. Dis. 12: 177 (Sept.) 1953.
- 700. Ford, L. T., and Key, J. A.: The differential diagnosis of shoulder, upper back and neck pain and the conservative treatment of cervical disc lesions, South. M. J. 47: 961 (Oct.) 1954.
- Ford, M. J., Watt, J., Hubbard, J. P., and Breese, B.: The prevention of rheumatic fever, Postgrad. Med. 15: 57 (Jan.) 1954.
- 702. Foreign letter: Research on rheumatism, J. A. M. A. 158: 685 (June 25) 1955.
- 703. Fortier, P. J.: Low back pain, J. Maine M. A. 46: 128 (May) 1955.
- Fourman, P.: Endocrine aspects of osteoporosis, Proc. Roy. Soc. Med. 48: 571 (July) 1955.
- Fox, H. M., Gifford, S., and Murawski, B. J.: Psychological effects of ACTH and cortisone, Connecticut M. J. 19: 453 (June) 1955.
- 706. Foxworthy, D. T., Poske, R. M., Barton, E. M., and Montgomery, M. M.: Adreno-corticotropin and cortisone in the treatment of severe Reiter's syndrome, J. Lab. and Clin. Med. 44: 797 (Nov.) 1954.
- Frain, J. B., and Morris, J. E.: Clinical experience with phenylbutazone (Butazolidin).
 Canad. M. A. J. 71: 445 (Nov.) 1954.
- 708. Frank, B. L.: More effective steroid therapy, Canad. M. A. J. 73: 410 (Sept. 1) 1955.
- 709. Frankel, C. J.: Aspiration biopsy of the spine, J. Bone and Joint Surg. 36A: 69 (Jan.) 1954.
- 710. Franklin, E. C., Holman, H. R., Müller-Eberhard, H. J., and Kunkel, H. G.: An unusual protein component of high molecular weight in the serum of certain patients with rheumatoid arthritis, J. Exper. Med. 105: 425 (May) 1957.
- Franklin, E. C., and Nemcik, F. J.: Shoulder dysfunction in pulmonary tuberculosis, Am. J. M. Sc. 227: 601 (June) 1954.
- 712. Fraser, J. R. E., and Barnett, A. J.: Thoracic outlet syndrome; case associated with short "first" rib, aneurysm of the subclavian artery and occlusion of brachial artery, M. J. Australia 2: 739 (Nov. 6) 1954.
- 713. Fraser, T. N.: Multiple toxic effects of phenylbutazone, report of a fatal case, Brit. M. J. 1: 1318 (May 28) 1955.
- 714. Frazer, E. H.: The use of traction in backache, M. J. Australia 2: 694 (Oct. 30) 1954.
- 715. Fredell, E. W., Johnson, H. P., Krupp, M. A., Engleman, E. P., and McGrath, A. K.: Adrenocortical function during long-term cortisone therapy, Arch. Int. Med. 95: 411 (Mar.) 1955.
- 716. Freeland, D. E., and Gribble, M. de G.: Hydrocortisone in tennis-elbow, Lancet 2: 225 (July 31) 1954.
- Freiberg, J. A.: Shoulder and arm pain associated with intrinsic and cervical lesions, Postgrad. Med. 16: 104 (Aug.) 1954.
- Fremont-Smith, P.: Bufferin in the management of rheumatoid arthritis, J. A. M. A. 158: 386 (June 4) 1955.
- 719. French, A. B., Migeon, C. J., Samuels, L. T., and Bowers, J. Z.: Effects of whole body x-irradiation on 17-hydroxycorticosteroid levels, leucocytes and volume of packed red cells in the Rhesus monkey, Am. J. Physiol. 182: 469 (Sept.) 1955.

- French, J. E., and Benditt, E. P.: Observations on the localization of alkaline phosphatase in healing wounds, Arch. Path. 57: 352 (Apr.) 1954.
- Freyberg, R. H.: The use of hormones in rheumatic diseases, J. Chron. Dis. 2: 559 (Nov.) 1955.
- 722. Friberg, S.: Lumbar disc degeneration in the problem of lumbago sciatica, Bull. Hosp. Joint Dis. 15: 1 (Apr.) 1954.
- Frick, P. G.: Acquired circulating anticoagulants in systemic "collagen disease," auto-immune thromboplastin deficiency, Blood 10: 691 (July) 1955.
- Fried, J.: Biological effects of 9-alpha-fluorohydrocortisone and related halogenated steroids in animals, Ann. New York Acad. Sc. 61: 573 (May 27) 1955.
- 725. Fried, J., and Sabo, E. F.: 9 a-fluoro derivatives of cortisone and hydrocortisone, J. Am. Chem. Soc. 76: 1455 (Mar. 5) 1954.
- Friedland, F.: Ultrasonic therapy with special reference to rheumatic diseases, Am. J. Phys. Med. 34: 379 (Apr.) 1955.
- Friedman, J., and Goldner, M. Z.: Discography in evaluation of lumbar disk lesions, Radiology 65: 653 (Nov.) 1955.
- Friedman, P. S.: Roentgen evaluation of the dynamics of low back pain, Pennsylvania M. J. 57: 143 (Feb.) 1954.
- Friedman, R. L., Russi, S., and Barry, W. F., Jr.: Clavicular changes associated with secondary hyperparathyroidism, Virginia M. Monthly 81: 261 (June) 1954.
- Frohner, R. N.: The enhancement of mephenesin action in the treatment of acute primary fibrositis, Am. Pract. and Digest Treat. 6: 1482 (Oct.) 1955.
- 731. Fruhman, G. J., and Gordon, A. S.: A quantitative study of adrenal influences upon the cellular elements of bone marrow, Endocrinology 57: 711 (Dec.) 1955.
- 732. Fudenberg, H., and Wintrobe, M. M.: Scleroderma with symptomatic hemolytic anemia: a case report, Ann. Int. Med. 43: 201 (July) 1955.
- 733. Fukushima, D. K., Leeds, N. S., Bradlow, H. L., Kritchevsky, T. H., Stokem, M. B., and Gallagher, T. F.: The characterization of four new metabolites of adrenocortical hormones, J. Biol. Chem. 212: 449 (Jan.) 1955.
- 734. Fulthorpe, A. J.: Agglutination of sheep erythrocytes sensitised with salmonella polysaccharides, J. Path. and Bact. 68: 315 (Oct.) 1954.
- 735. Furlong, R.: The frozen shoulder, Practitioner 173: 90 (July) 1954.
- 736. Fyfe, W. M.: Rheumatoid arthritis in childhood, Glasgow M. J. 36: 102 (Mar.) 1955.
- 737. Gabriel, J. B., Katz, H. M., Reiman, J., and Luger, N. M.: DCA-like effects of Butazolidin in normal subjects and in a patient with Addison's disease, Metabolism 4: 119 (Mar.) 1955.
- 738. Gaebler, O. H., Beher, W. T., Sigler, J. W., and Galpin, R. R.: Reproducibility and validity of sodium sulfate fractionation of proteins in plasma and knee joint fluid, Clin. Chem. 1: 105 (Apr.) 1955.
- Galli, T., and Chiti, E.: Rheumatoid arthritis and plasmacytomatosis, Ann. Rheumat. Dis. 14: 271 (Sept.) 1955.
- Gamble, C. N., and Brunson, J. G.: Experimental fibrinoid lesions in rabbits, production by cross transfusion and isolated renal perfusion, Arch. Path. 60: 583 (Dec.) 1955.
- 741. Gandler, A. L.: Management of degenerative joint disease, M. Times, New York 83: 488 (May) 1955.
- 742. Gardell, S., and Rastgeldi, S.: On the mucopolysaccharides of nucleus pulposus, Acta chem. Scand. 8: 362, 1954.
- 743. Gardiner, T. B.: Osteochondritis dissecans in three members of one family, J. Bone and Joint Surg. 37B: 139 (Feb.) 1955.
- 744. Gardner, E. D.: Physiology of blood and nerve supply of joints, Bull. Hosp. Joint Dis. 15: 35 (Apr.) 1954.
- 745. Garland, L. H., and Sisson, M. A.: Pulmonary roentgenologic changes in the collagen diseases, Am. J. Surg. 90: 63 (July) 1955.

- 746. Garland, L. H., and Sisson, M. A.: Roentgen findings in the "collagen" diseases, Am. J. Roentgenol. 71: 581 (Apr.) 1954.
- 747. Garrod, O., Nabarro, J. D. N., Pawan, G. L. S., and Walker, G.: Metabolic effects of 9 a-fluorohydrocortisone and of cortisone in adrenal insufficiency, Lancet 2: 367 (Aug. 20) 1955.
- 748. Gartner, S., and Rubner, K.: Calcified scleral nodules in hypervitaminosis D, Am. J. Ophth. 39: 658 (May) 1955.
- Gastineau, C. F.: Postoperative adrenal cortical insufficiency, M. Bull. U. S. Army, Europe 12: 43 (Feb.) 1955.
- 750. Gaulhofer, W. K.: The effect of cortisone on Sjögren's syndrome, Acta med. Scandinav. 149: 441, 1954.
- Gayral, L., and Neuwirth, E.: Oto-neuro-ophthalmologic manifestations of cervical origin, New York State J. Med. 54: 1920 (July 1) 1954.
- 752. Gear, J.: Autoantibodies and the hyper-reactive state in the pathogenesis of disease, Acta med. Scandinay. Supp. 306: 39, 1955.
- 753. Gedda, P. O.: On amyloidosis and other causes of death in rheumatoid arthritis.

 Acta med. Scandinav, 150: 443, 1955.
- 754. Geertruyden, M. B., Danis, P., and Toussaint, C.: Fundus lesions with disseminated lupus erythematosus, Arch. Ophth. 51: 799 (June) 1954.
- 755. Gelber, A.: Erythema multiforme following phenylbutazone treatment for arthritis, J. Am. M. Women's A. 9: 361 (Nov.) 1954.
- 756. Gelber, J., and Byron, R. J.: Treatment of osteitis pubis with corticotropin and cortisone, report of two cases, Arch. Surg. 69: 543 (Oct.) 1954.
- 757. Gelber, L. J.: Functional restoration of the shoulder by deep x-ray therapy in bursitis, New York State J. Med. 54: 2971 (Nov. 1) 1954.
- 758. Gelbke, H.: Intra-articular bone-graft resorption in transarticular bone-graft arthrodesis, Arch. Surg. 68: 633 (May) 1954.
- 759. Genkins, G., Uhr, J. W., and Bryer, M. S.: Bacitracin nephropathy, report of a case of acute renal failure and death, J. A. M. A. 155: 894 (July 3) 1954.
- 760. Gentry, J. T., Nitowsky, H. M., and Michael, M., Jr.: Studies on the epidemiology of sarcoidosis in the United States: the relationship to soil areas and to urban-rural residence, J. Clin. Investigation 34: 1839 (Dec.) 1955.
- 761. Germuth, F. G., Jr., Pace, M. G., and Tippett, J. C.: Comparative histologic and immunologic studies in rabbits of induced hypersensitivity of the serum sickness type. II. The effect of sensitization to homologous and cross-reactive antigens on the rate of antigen elimination and the development of allergic lesions, J. Exper. Med. 101: 135 (Feb.) 1955.
- 762. Gershon-Cohen, J., Schraer, H., and Blumberg, N.: Bone density measurements of osteoporosis in the aged, Radiology 65: 416 (Sept.) 1955.
- 763. Gershon-Cohen, J., Boreadis, A. G., and Glauser, F.: Luschka joints of the cervical spine with relation to nerve root irritation, J. Albert Einstein M. Center 3: 29 (Nov.) 1954.
- 764. Gershon-Cohen, J., Schraer, H., and Blumberg, N.: Posterior and anterior spondylo-listhesis in the aged, Geriatrics 9: 327 (July) 1954.
- 765. Gersten, J. W.: Changes in hydration of muscle and tendon following the application of ultrasonic energy, Arch. Phys. Med. 36: 140 (Mar.) 1955.
- 766. Gersten, J. W.: Effect of ultrasound on tendon extensibility, Am. J. Phys. Med. 34: 362 (Apr.) 1955.
- 767. Gersten, J. W.: Ultrasonics and muscle disease, Am. J. Phys. Med. 33: 68 (Feb.) 1954.
- 768. Gewalli, N.: Experiences of prolonged cortisone and ACTH treatment in rheumatoid arthritis, Acta med. Scandinav. 148: 291 (Apr.) 1954.
- 769. Ghormley, R. K., and Romness, J. O.: Pigmented villonodular synovitis (xanthomatosis) of the hip joint, Proc. Staff Meet., Mayo Clin. 29: 171 (Mar. 24) 1954.

- Giannestras, N.: Legg-Perthes disease in twins, J. Bone and Joint Surg. 36A: 149 (Jan.) 1954.
- Gibson, A.: Hyaline cartilage: degeneration and regeneration, Canad. M. A. J. 73: 442 (Sept. 15) 1955.
- 772. Gibson, M. L., and Cawley, P. T.: An evaluation of laboratory aids in the diagnosis of rheumatic fever, Bull. Denver Rheumat. Fever Diagnostic Service 1: #4 (Nov.) 1955
- 773. Gibson, T., and Davis, W. B.: Some further observations on the use of preserved animal cartilage, Brit. J. Plast. Surg. 8: 85 (July) 1955.
- 774. Gil, J. R., Rodriguez, H., and Ibarra, J. J.: Incidence of asymptomatic, active rheumatic cardiac lesions in patients submitted to mitral commissurotomy and the effect of cortisone on these lesions, Am. Heart J. 50: 912 (Dec.) 1955.
- Giles, R. B., Jr., and Calkins, E.: Studies of the composition of secondary amyloid,
 J. Clin. Inevstigation 34: 1476 (Sept.) 1955.
- Gill, G. G., and White, H. L.: Mechanisms of nerve-root compression and irritation in backache, Clin. Orthop. 5: 66, 1955.
- 777. Gillette, R., and Buchsbaum, R.: Alteration in fibroblastosis treated with steroids in a perfusion chamber, Proc. Soc. Exper. Biol. and Med. 89: 146 (May) 1955.
- Gilliland, I. C., and Manning, G. C.: Liver abscess and polyarteritis nodosa, Brit. M. J. 2: 794 (Oct. 2) 1954.
- 779. Gilliland, I. C., and Stanton, E.: Protein and protein-bound polysaccharide abnormalities in the diagnosis of amyloid and allied disorders by paper electrophoresis, J. Clin. Path. 7: 172 (May) 1954.
- 780. Gillman, T., Penn, J., Bronks, D., and Roux, M.: Abnormal elastic fibers, appearance in cutaneous carcinoma, irradiation injuries, and arterial and other degenerative connective tissue lesions in man, Arch. Path. 59: 733 (June) 1955.
- Gillmor, C. S., and Cramer, Q.: Rheumatoid spondylitis, Missouri Med. 51: 994 (Dec.) 1954.
- 782. Gilmore, H. R., and Stecher, R. M.: Rheumatoid arthritis and spondylitis. The clinical history and the pathological changes after twenty years of disability, Military Med. 117: 432 (Nov.) 1955.
- Gilpin, W. A.: Treatment of rheumatoid arthritis and osteoarthritis with succinatesalicylate, J. Michigan M. Soc. 54: 1428 (Dec.) 1955.
- 784. Gilston, R. J.: Clubbing, GP 11: 94 (Feb.) 1955.
- 785. Gilston, R. J.: Felty's syndrome, GP 11: 97 (June) 1955.
- Gingrass, R. P.: Chondrosarcoma of the mandibular joint: report of case, J. Oral Surg. 12: 61 (Jan.) 1954.
- 787. Gjessing, H. G. A.: Scleromalacia perforans treated with cortisone, Acta ophth. 33: 229, 1955.
- 788. Gjørup, S., and Poulsen, H.: Effects of probenecid, cinchophen and colchicine of the plasma concentration and renal excretion of oxypurine in patients with gout, Acta pharmacol. et toxicol. 11: 343, 1955.
- 789. Gjørup, S., Poulsen, H., and Praetorius, E.: The uric acid concentration in serum determined by enzymatic spectrophotometry, Scandinav. J. Clin. and Lab. Invest. 7: 201, 1955.
- Glaser, G. H., Kornfeld, D. S., and Knight, R. P., Jr.: Intravenous hydrocortisone, corticotropin and the electroencephalogram, Arch. Neurol. and Psychiat. 73: 338 (Mar.) 1955.
- 791. Gleason, D. F., Street, J. P., and Kahn, K. A.: Effects of pyrazinamide on serum and urine uric acid, J. Lab. and Clin. Med. 48: 810 (Nov.) 1956.
- 792. Gleckler, W. J.: Rheumatoid spondylitis with carditis, Am. J. Med. 16: 284 (Feb.)

- 793. Glegg, R. E., Edinger, D., and Leblond, C. P.: Presence of carbohydrates distinct from acid mucopolysaccharides in connective tissue, Science 120: 839 (Nov. 19) 1954.
- 794. Godman, G. C., and Churg, J.: Wegener's granulomatosis, pathology and review of the literature, Arch. Path. 58: 533 (Dec.) 1954.
- 795. Godtfredsen, E.: Ophthalmological signs and symptoms in mesenchymal diseases, Acta ophth. 32: 717, 1954.
- 796. Göthman, B., and Nordström, S.: A case of bilateral osteochondritis dissecans of the lateral condyle of the tibia, Acta chir. Scandinav. 107: 128, 1954.
- 797. Goetzee, A. E., and Williams, H. O.: A case of Dupuytren's contracture involving the hand and foot in a child, Brit. J. Surg. 42: 417 (Jan.) 1955.
- 798. Goff, C. W.: Growth acceleration in Legg-Calvé-Perthes' syndrome by complementary feedings of Aureomycin, Clin. Orthop. 6: 95, 1955.
- 799. Goff, C. W.: Have you a backache?, Connecticut M. J. 19: 184 (Mar.) 1955.
- 800. Gold, A. M.: Synovial sarcoma of the shoulder region, Bull. Hosp. Joint Dis. 15: 79 (Apr.) 1954.
- Gold, S. C.: An unusual papular eruption associated with lupus erythematosus, Brit. J. Dermat. 66: 429 (Dec.) 1954.
- 802. Golderos, A. F.: Abacterial urethritis, abacterial pyuria and Reiter's syndrome, J. Urol. 73: 536 (Mar.) 1955.
- 803. Goldfain, E., and Huffman, M. N.: A study of the action of pregnenolone methyl ether in patients with rheumatoid arthritis, Acta med. Scandinav. 147: 455, 1954.
- 804. Goldfien, A., Laidlaw, J. C., Haydar, N. A., Renold, A. E., and Thorn, G. W.: Fluorohydrocortisone and chlorohydrocortisone, highly potent derivatives of compound F, New England J. Med. 252: 415 (Mar. 17) 1955.
- 805. Goldfien, A., Morse, W. I., Froesch, E. R., Ganong, W. F., Renold, A. E., and Thorn, G. W.: Pharmacological studies in man of 11-, 17-, and 21-hydroxy derivatives of progesterone and their fluorinated analogs, Ann. New York Acad. Sc. 61: 433 (May 27) 1955.
- 806. Goldman, I. R., Young, J. M., and Knox, F. H.: Myocardial involvement in generalized scleroderma, Dis. of Chest 25: 94 (Jan.) 1954.
- 807. Goldman, L., Flatt, R., and Baskett, J.: Assay technics for local anti-inflammatory activity in the skin of man as applied to 9A fluorohydrocortisone acetate and free alcohol, J. Invest. Dermat. 24: 81 (Feb.) 1955.
- 808. Goldman, L.: Histological effects of hydrocortisone in the skin of man, Ann. New York Acad. Sc. 61: 520 (May 27) 1955.
- Goldman, S. E., and Eibel, P.: Isonicotinic acid hydrazide in the treatment of tuberculous tenosynovitis, Canad. M. A. J. 71: 254 (Sept.) 1954.
- 810. Goldsmith, W. N.: Cortisone and corticotrophin in dermatology, Practitioner 175: 569 (Nov.) 1955.
- 811. Goltz, R. W., and Laymon, C. W.: Multicentric reticulohistiocytosis of the skin and synovia, reticulohistiocytoma or ganglioneuroma, Arch. Dermat. and Syph. 69: 717 (June) 1954.
- 812. Gomori, G.: The histochemistry of mucopolysaccharides, Brit. J. Exper. Path. 35: 377 (Aug.) 1954.
- 813. Goodson, W. H., Jr., Rose, D. L., and Alyea, W. S.: The use of trypsin in rheumatoid arthritis: a clinical study, J. Kansas M. Soc. 55: 129 (Mar.) 1954.
- 814. Gordon, L., and Lowenstein, L.: A case of acquired haemolytic anaemia with features resembling lupus erythematosus, Canad. M. A. J. 73: 207 (Aug. 1) 1955.
- 815. Gordon, S.: Dupuytren's contracture: the significance of various factors in its etiology, Ann. Surg. 140: 683 (Nov.) 1954.
- 816. Gorham, L. W., Wright, A. W., Shultz, H. H., and Maxon, F. C., Jr.: Disappearing bones: a rare form of massive osteolysis, Am. J. Med. 17: 674 (Nov.) 1954.

- 817. Gorham, L. W., and Stout, A. P.: Hemangiomatosis and its relation to massive osteolysis, Tr. A. Am. Physicians 67: 302, 1954.
- 818. Gorham, L. W., and Stout, A. P.: Massive osteolysis (acute spontaneous absorption of bone, phantom bone, disappearing bone); its relation to hemangiomatosis, J. Bone and Joint Surg. 37A: 985 (Oct.) 1955.
- 819. Gornall, A. G.: Steroid hormones and arthritis, First Canadian Conference on Research on Rheumatic Diseases, Toronto, March, 1955, p. 21.
- Gorrell, R. L.: Procaine injections for painful musculoskeletal conditions, Journal Lancet 75: 32 (Jan.) 1955.
- 821. Goslings, J., Querido, A., Cats, A., and Kassenaar, A.: Evaluation of corticotrophine (ACTH) in patients, Acta med. Scandinav. 148: 343, 1954.
- 822. Gough, J., Rivers, D., and Seal, R. M. E.: Pathological studies of modified pneumoconiosis in coal-miners with rheumatoid arthritis (Caplan's syndrome), Thorax 10: 9 (Mar.) 1955.
- 823. Gould, D. M., and Daves, M. L.: Roentgenologic findings in systemic lupus erythematosus, J. Chron. Dis. 2: 136 (Aug.) 1955.
- 824. Gould, I. D.: Rheumatoid arthritis aggravated by pregnancy and controlled by cortisone, New York State J. Med. 55: 1164 (Apr. 15) 1955.
- 825. Goulding, R., MacLean, K. S., and Robson, J. M.: Clinical investigation of alleged antagonism of corticoids, Lancet 2: 775 (Oct. 16) 1954.
- Graham, W.: Fibrositis and non-articular rheumatism, Physiotherapy 40: 101 (Apr.) 1954.
- Graham, W.: Fibrositis and non-articular rheumatism, Physiotherapy Rev. 35: 128 (Mar.) 1955.
- 828. Graham, W., and Graham, K. M.: Our gouty past, Canad. M. A. J. 73: 485 (Sept. 15) 1955.
- Graubard, D. J.: Dupuytren's contracture, J. Internat. Coll. Surgeons 21: 15 (Jan.) 1954.
- 830. Gray, J. W., and Merrick, E. Z.: The clinical evaluation of Meticorten in rheumatoid arthritis and allied conditions, J. Am. Geriatrics Soc. 3: 337 (May) 1955.
- 831. Gray, S. J., Ramsey, C., and Reifenstein, R. W.: Hormonal influences upon the stomach, Am. J. Gastroenterol. 24: 244 (Sept.) 1955.
- 832. Grebe, A. A.: Monostotic coccidioidal infection: report of a case successfully treated with 2-hydroxystilbamidine, J. Bone and Joint Surg. 36A: 859 (July) 1954.
- 833. Greenberg, G. R.: Role of folic acid derivatives in purine biosynthesis, Federation Proc. 13: 745 (Sept.) 1954.
- 834. Greenman, L., Weigand, F. A., Mateer, F. M., and Danowski, T. S.: Cortisone therapy of initial attacks of rheumatic carditis. I. Clinical data, Am. J. Dis. Child. 89: 426 (Apr.) 1955.
- 835. Greenman, L., Weigand, F. A., Mateer, F. M., and Danowski, T. S.: Cortisone therapy of initial attacks of rheumatic carditis. II. Laboratory findings, Am. J. Dis. Child. 89: 442 (Apr.) 1955.
- Greenspan, E. M.: Clinical significance of serum mucoproteins, Advances Int. Med. 7: 101, 1955.
- Greenspan, E. M.: Survey of clinical significance of serum mucoprotein level, Arch. Int. Med. 93: 863 (June) 1954.
- Greenstein, G. H., and Buchman, J.: Experiences with nylon hip prosthesis, Bull. Hosp. Joint Dis. 15: 251 (Oct.) 1954.
- 839. Greenstein, N. M.: Corticotropin in rheumatic carditis, beneficial effects of high dosage and short duration in acute exacerbations of chronic rheumatic carditis, Am. J. Dis. Child. 87: 694 (June) 1954.
- 840. Greenstein, R. H., and Cahn, M. M.: Essential thrombocytopenia as an early manifestation of systemic lupus erythematosus, J. Albert Einstein M. Center 2: 113 (May) 1954.

- 841. Gribble, M. de G.: Rheumatoid arthritis and psoriasis, Ann. Rheumat. Dis. 14: 198 (June) 1955.
- 842. Grokoest, A. W., and Demartini, F. E.: Systemic disease and the carpal tunnel syndrome, J. A. M. A. 155: 635 (June 12) 1954.
- 843. Gross, J., Highberger, J. H., and Schmitt, F. O.: Collagen structures considered as states of aggregation of a kinetic unit. The tropocollagen particle, Proc. Nat. Acad. Sc. 40: 679 (Aug.) 1954.
- 844. Gross, J.: Some structural and chemical properties of connective tissue,—Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 149.
- 845. Grossfeld, H., and Ragan, C.: Action of hydrocortisone on cells in tissue culture, Proc. Soc. Exper. Biol. and Med. 86: 63 (May) 1954.
- 846. Grossfeld, H., Meyer, K., and Godman, G.: Differentiation of fibroblasts in tissue culture, as determined by mucopolysaccharide production, Proc. Soc. Exper. Biol. and Med. 88: 31 (Jan.) 1955.
- 847. Grynbaum, B. B.: An evaluation of the clinical use of ultrasonics, Am. J. Phys. Med. 33: 75 (Feb.) 1954.
- 848. Grynbaum, B. B., and Russek, A. S.: Evaluation of 300 cases of shoulder pain, Arch. Phys. Med. 36: 35 (Jan.) 1955.
- 849. Gsell, O. R.: Agranulocytosis associated with phenylbutazone therapy, Internat. Rec. Med. 167: 483 (Sept.) 1954.
- 850. Gueft, B., and Laufer, A.: Further cytochemical studies in systemic lupus erythematosus, Arch. Path. 57: 201 (Mar.) 1954.
- Gulotta, G. A., Peterson, W. L., and Daniels, R. S.: The Q-Tc, an aid to the diagnosis of rheumatic carditis, U. S. Armed Forces M. J. 6: 162 (Feb.) 1955.
- 852. Gurling, K. J., Bruce-Pearson, R. S., and Pond, M. H.: Sjögren's syndrome treated with ACTH, Brit. J. Ophth. 38: 619 (Oct.) 1954.
- 853. Gustavson, K. H.: The function of hydroxyproline in collagens, Nature, London 175:70 (Jan. 8) 1955.
- 854. Gutman, A. B., Yü, T. F., and Randolph, V.: Further observations on the uricosuric effects of probenecid (Benemid) in tophaceous gout, Tr. A. Am. Physicians 67: 250, 1954.
- 855. Gutman, A. B., and Yü, T. F.: Prevention and treatment of chronic gouty arthritis, J. A. M. A. 157: 1096 (Mar. 26) 1955.
- 856. Gutman, A. B.: Primary and secondary gout, Ann. Int. Med. 39: 1062 (Nov.) 1953.
- 857. Gutman, A. B., Yü, T. F., and Sirota, J. H.: A study, by simultaneous clearance techniques, of salicylate excretion in man. Effect of alkalinization of the urine by bicarbonate administration; effect of probenecic, J. Clin. Investigation 34: 711 (May) 1955.
- 858. Gutstein, R. R.: The pelvic girdle syndrome: the role of pelvic girdle and crural triggers and fibrositis in functional disorders of the lower limbs, including cramps, restlessness, swelling of the legs and hyperhidrosis of the feet, Am. Pract. and Digest Treat. 6: 365 (Mar.) 1955.
- 859. Gutstein, R. R.: A review of myodysneuria (fibrositis): the role of myodysneuria in cutaneous vasomotor disorders including menopausal hot flashes, sebaceous and sudatory abnormalities. A review of the role of abdominal and dorsolumbar triggers in functional gastro-intestinal diseases, Am. Pract. and Digest Treat. 6: 570 (Apr.) 1955.
- 860. Hackett, G. S., and Henderson, D. G.: Joint stabilization, an experimental, histologic study with comments on the clinical application in ligament proliferation, Am. J. Surg. 89: 968 (May) 1955.

- Hadley, L. A.: Bony masses projecting into the spinal canal opposite a break in the neural arch of the fifth lumbar vertebra, J. Bone and Joint Surg. 37A: 787 (July) 1955.
- 862. Hadley, L. A.: Fatigue fracture of the fifth lumbar neural arch, is spondylolysis a stress fracture?, Clin. Orthop. 6: 110, 1955.
- 863. Hadley, L. A.: Studies on spondylolisthesis, Am. J. Roentgenol. 71: 488 (Mar.) 1954. 864. Hagerman, G.: Infection, allergy and the pathogenesis of rheumatic disease, Acta
- 864. Hagerman, G.: Infection, allergy and the pathogenesis of rheumatic disease, Acta Rheum. Scandinav. 1: 209, 1955.
- 865. Haggart, G. E., and Terheyden, W. A.: The present management of disk lesions in the lumbar spine, S. Clin. North America 35: 859 (June) 1955.
- 866. Haggart, G. E., and Hammond, G.: Treatment of degenerative arthritis of the hip joint in older patients, S. Clin. North America, 34: 829 (June) 1954.
- 867. Haight, T. H., Ziegra, S. R., and Kahn, F. H.: Erythromycin therapy of respiratory infections. II. Effects of varying durations of therapy of streptococcal infections on eradication of streptococci and on formation of antistreptolysis O, Antibiotics and Chemotherapy 4: 439 (Apr.) 1954.
- Hakim, J., and Ricca, J. J.: Jaundice following phenylbutazone therapy, New York State J. Med. 55: 2206 (Aug. 1) 1955.
- Halbert, S. P., Swick, L., and Sonn, C.: The use of precipitin analysis in agar for the study of human streptococcal infections. I. Oudin technic, J. Exper. Med. 101: 539 (May) 1955.
- Halbert, S. P., Swick, L., and Sonn, C.: The use of precipitin analysis in agar for the study of human streptococcal infections. II. Ouchterlony and Oakley technics, J. Exper. Med. 101: 557 (May) 1955.
- 871. Hald, J.: Treatment of bone and joint tuberculosis with streptomycin and P. A. S., Acta tuberc. Scandinav. 30: 82, 1954.
- 872. Hall, D. A., Keech, M. K., Reed, R., Saxl, H., Tunbridge, R. E., and Wood, M. J.: Collagen and elastin in connective tissue, J. Gerontol. 10: 388 (Oct.) 1955.
- 873. Hall, D. A., Reed, R., and Tunbridge, R. E.: Electron microscope studies of elastic tissue, Exper. Cell Res. 8: 35, 1955.
- 874. Hall, D. A.: The reaction between elastase and elastic tissue. I. The substrate, Biochem. J. 59: 459 (Mar.) 1955.
- 875. Hall, D. A., and Gardiner, J. E.: The reaction between elastase and elastic tissue. II. Preparation and properties of the enzyme, Biochem. J. 59: 465 (Mar.) 1955.
- 876. Hall, R. M.: Regeneration of the lower femoral epiphysis; report of a case, J. Bone and Joint Surg. 36B: 116 (Feb.) 1954.
- 877. Hallock, H., and Jones, J. B.: Tuberculosis of the spine: an end-result study of the effects of the spine-fusion operation in a large number of patients, J. Bone and Joint Surg. 36A: 219 (Apr.) 1954.
- 878. Hall-Smith, S. P.: Psoriasis and lupus erythematosus, Brit. J. Dermat. 67: 227 (June) 1955.
- 879. Ham, A. W.: Mechanism of nutrition in bone, its effect on growth, repair and transplantation, in Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conference, September, 1955, Hospital for Special Surgery, New York, p. 145.
- 880. Hammarsten, G., and Jonsson, E.: Investigation of the enzymatic activity in rheumatoid arthritis. I. The activity of plasmin in plasma from patients with rheumatoid arthritis, Acta med. Scandinav. 147: 359, 1954.
- 881. Hammarsten, G., and Jonsson, E.: Investigation of the enzymatic activity in rheumatoid arthritis. II. The antiplasmin action of serum in patients with rheumatoid arthritis, Acta med. Scandinav. 147: 363, 1954.
- 882. Hamwi, G. J., and Goldberg, R. F.: Clinical use of fludrocortisone acetate, J. A. M. A. 159: 1598 (Dec. 24) 1955.

- 883. Hanes, C. B.: Evaluation of a non-narcotic analgesic preparation in private general practice, Am. Pract. and Digest Treat. 6: 602 (Apr.) 1955.
- 884. Hanisch, C. M.: Myositis ossificans of paravertebral region, Bull. Hosp. Joint Dis. 16: 58 (Apr.) 1955.
- 885. Hanns, W. H., and Sherman, M. S.: "Xanthomas" of tendon sheaths, J. Louisiana M. Soc. 107: 453 (Nov.) 1955.
- 886. Hanrahan, G. E.: Three cases of disseminated lupus erythematosus with psychosis. Canad. M. A. J. 71: 374 (Oct.) 1954.
- 887. Hansen, J. L.: Proc. 3rd Internat. Congr. Dis. Chest, 1954.
- 888. Hansen, K. B., Fischer, F., and Brøchner-Mortensen, K.: Treatment of rheumatoid arthritis with cortisone (two- to four-year studies), Acta. Rheum. Scandinav. 1: 7, 1955.
- 889. Hansson, K. G., and Austlid, O.: Myositis ossificans in poliomyelitis: two case reports, Arch. Phys. Med. 36: 506 (Aug.) 1955.
- Hargraves, M. M.: Systemic lupus erythematosus and L. E. cell phenomenon, Postgrad. Med. 16: 164 (Sept.) 1954.
- Harkness, A. H.: Arthritis associated with non-gonococcal urethritis, Rheumatism 10: 91 (Oct.) 1954.
- 892. Harkness, R. D., Marko, A. M., Muir, H. M., and Neuberger, A.: The metabolism of collagen and other proteins of the skin of rabbits, Biochem. J. 56: 558 (Apr.) 1954.
- 893. Harnagel, E. E., and Kramer, W. G.: Severe adrenocortical insufficiency following joint manipulation, report of patient receiving cortisone orally, J. A. M. A. 158: 1518 (Aug. 27) 1955.
- 894. Harper, F. R., and Patterson, L. T.: Osteoarthropathy in carcinoma of the lung, Arch. Surg. 70: 643 (May) 1955.
- 895. Harris, C., Jr., and Riordan, D. C.: Intrinsic contracture in the hand and its surgical treatment, J. Bone and Joint Surg. 36A: 10 (Jan.) 1954.
- 896. Harris, H.: The sulphur requirement of rat connective tissue cells, Brit. J. Exper. Path. 36: 454 (Oct.) 1955.
- 897. Harris, L. H.: Pulmonary manifestations of "rheumatoid disease," Lancet 2: 119 (July 17) 1954.
- 898. Harris, R., and Millard, J. B.: Paraffin-wax baths in the treatment of rheumatoid arthritis, Ann. Rheumat. Dis. 14: 278 (Sept.) 1955.
- 899. Harris, R. I., and MacNab, I.: Structural changes in the lumbar intervertebral discs: their relationship to low back pain and sciatica, J. Bone and Joint Surg. 36B: 304 (May) 1954.
- Harris, S. B., and Klein, R.: Hematologic observations in short and long-term treatment of rheumatic diseases with phenylbutazone, New York State J. Med. 55: 95 (Jan. 1) 1955.
- Harris, T. N.: Etiologic factors in rheumatic fever, M. Clin. North America 38: 1693 (Nov.) 1954.
- 902. Harris, T. N., Harris, S., and Ogburn, C. A.: Gel-precipitation of streptococcal culture supernates with sera of patients with rheumatic fever and streptococcal infection, Proc. Soc. Exper. Biol. and Med. 90: 39 (Oct.) 1955.
- Harris-Jones, J. N.: Disseminated lupus erythematosus, Medicine Illus. (London)
 657 (Oct.) 1954.
- 904. Harrison, M. H. M.: Dupuytren's contracture of hands and feet, Proc. Roy. Soc. Med. 48: 164 (Mar.) 1955.
- Harrison, M. H. M.: Present trends in the treatment of osteoarthritis of the hip. Post-Grad. M. J. 31: 397 (Aug.) 1955.
- 906. Harrison, R. G., and Gossman, H. H.: The fate of radiopaque media injected into the cancellous bone of the extremities, J. Bone and Joint Surg. 37B: 150 (Feb.) 1955.

- Harrold, A. J.: Tuberculosis of the spine, a reassessment of the problem and the results of conservative treatment, Post-Grad. M. J. 31: 495 (Oct.) 1955.
- 908. Hart, F. D.: Ankylosing spondylitis: a survey, Ann. Rheumat. Dis. 13: 186 (Sept.) 1954.
- 909. Hart, F. D.: Ankylosing spondylitis, Ann. Rheumat. Dis. 14: 77 (Mar.) 1955.
- Hart, F. D.: Clinical uses of intravenous hydrocortisone, Brit. M. J. 1: 454 (Feb. 19) 1955.
- Hart, F. D., Watkins, M., Burley, D., and Richards, M. T.: Osteoarthritis and rest, Brit. M. J. 2: 269 (July 31) 1954.
- 912. Hart, F. D.: Osteoarthritis, degenerative joint disease, Medicine Illus. (London) 9: 284 (May) 1955.
- 913. Hart, F. D., Clark, C. J. M., and Golding, J. R.: Prednisone and prednisolone in the treatment of rheumatoid arthritis, Lancet 2: 998 (Nov. 12) 1955.
- 914. Hart, F. D., and Mackenzie, D. H.: Pulmonary rheumatoid disease, Brit. M. J. 2: 890 (Oct. 8) 1955.
- 915. Hart, F. D.: The rarer arthropathies, Post-Grad. M. J. 31: 627 (Dec.) 1955.
- Hart, F. D.: The treatment of ankylosing spondylitis, Proc. Roy. Soc. Med. 48: 207 (Mar.) 1955.
- 917. Hart, M.: Pain in the neck, based on a study of 100 cases, Ann. Phys. Med. 2: 90 (July) 1954.
- Hartfall, S. J.: Cortisone and corticotrophin in chronic rheumatic diseases and gout, Practitioner 175: 553 (Nov.) 1955.
- 919. Hartfall, S. J.: Stress and the rheumatic disorders, Practitioner 172: 29 (Jan.) 1954.
- Hartfall, S. J.: Stress factors in the aetiology of the rheumatic diseases, Brit. J. Phys. Med. 18: 16 (Jan.) 1955.
- 921. Hartfall, S. J.: Stress factors in the aetiology of the rheumatic diseases, Physiotherapy 40: 339 (Nov.) 1954.
- Hartiala, K. J. V., Kassinen, A., and Suutarinen, H.: The beneficial effect of estrogens on experimental cinchophen ulcer, Ann. med. exper. et biol. Fenniae 32: 444, 1954.
- 923. Hartiala, K. J. V., and Telivuo, L.: Studies on detoxication mechanisms. II. Effect of cinchophen on the glucuronide synthesis by the liver, Ann. med. exper. et biol. Fenniae 33: 219, 1955.
- Hartley, J.: Reflex hyperemic deossification (Sudeck's atrophy), J. Mt. Sinai Hosp.
 22: 268 (Nov.-Dec.) 1955.
- Hartung, E. F.: History of the use of colchicum and related medicaments in gout, Ann. Rheumat. Dis. 13: 190 (Sept.) 1954.
- 926. Hartung, E. F.: Tuberculous arthritis, J. A. M. A. 158: 818 (July 9) 1955.
- 927. Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic lupus erythematosus, review of the literature and clinical analysis of 138 cases, Medicine 33: 291 (Dec.) 1954.
- Haserick, J. R.: Modern concepts of systemic lupus erythematosus: a review of 126 cases, J. Chron. Dis. 1: 317 (Mar.) 1955.
- 929. Hauge, B. N., and Christiansen, T.: Weber-Christian's disease, a survey with report of a case, Acta med. Scandinav. 150: 193, 1954.
- Hauge, M., and Harvald, B.: Heredity in gout and hyperuricemia, Acta med. Scandinav. 152: 247, 1955.
- Haydu, G. G.: The inhibition of adenosintriphosphatase activity in rheumatoid arthritis, Rheumatism 10: 32 (Apr.) 1954.
- 932. Haydu, G. G.: Modification of the niacin furfuryl reaction by diphosphopyridin nucleotide in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 177, 1955.
- 933. Heathfield, K. W. G.: Peripheral neuritis, Medicine Illus. (London) 9: 496 (Aug.) 1955.
- 934. Heathfield, K. W. G., and Williams, J. R. B.: Peripheral neuropathy in periarteritis nodosa, Lancet 2: 673 (Oct. 2) 1954.

- 935. Hechter, O., and Pincus, G.: Genesis of the adrenocortical secretion, Physiol. Rev. 34: 459 (July) 1954.
- 936. Heck, C. V., and Chandler, F. A.: Diagnosis and treatment of pain in the acromic-clavicular joint, J. Am. Geriatrics Soc. 3: 993 (Dec.) 1955.
- 937. Heerup, A.: Boy aged 10 years suffering from dermatomyositis, Acta paediat. 44: 93 (Jan.) 1955.
- 938. Heffer, E. T., Turin, R. D., Slater, S. R., and Kroop, I. G.: An evaluation of large doses of cortisone in first attacks of rheumatic carditis, J. Pediat. 44: 630 (June) 1954.
- 939. Heller, G., Jacobson, A. S., Kolodny, M. H., and Kammerer, W. H.: The hemagglutination test for rheumatoid arthritis. II. The influence of human plasma fraction II (gamma globulin) on the reaction, J. Immunol. 72: 66 (Jan.) 1954.
- 940. Heller, G., Kolodny, M. H., Lepow, I. H., Jacobson, A. S., Rivera, M. E., and Marks, G. H.: The hemagglutination test for rheumatoid arthritis. IV. Characterization of the rheumatoid agglutinating factors by analysis of serum fractions prepared by ethanol fractionation, J. Immunol. 74: 340 (May) 1955.
- 941. Heller, J. H.: Cortisone and phagocytosis, Endocrinology 56: 80 (Jan.) 1955.
- 942. Hellier, F. F.: Cortisone and ACTH in dermatology, Practitioner 172: 503 (May) 1954.
- 943. Hellman, L., Bradlow, H. L., Adesman, J., Fukushima, D. K., Kulp, J. L., and Gallagher, T. F.: The fate of hydrocortisone-4-C¹⁴ in man, J. Clin. Investigation 33: 1106 (July) 1954.
- 944. Hench, P. S.: The cortisones and corticotropins in general medicine with special reference to the rheumatic diseases, in Lectures on orthopaedics and rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conference, September, 1955, Hospital for Special Surgery, New York, p. 177.
- Henderson, E.: New developments in steroid therapy of rheumatic diseases, J. M. Soc. New Jersey 52: 609 (Dec.) 1955.
- 946. Henderson, R. G., and Main, R. G.: Malignant tenosynovioma (fibrosarcoma) with twenty-three years' survival, Brit. J. Surg. 42: 268 (Nov.) 1954.
- 947. Hendricks, A. B.: Protean manifestations of periarteritis nodosa, J. Iowa M. Soc. 45: 75 (Feb.) 1955.
- 948. Henn, M. J., Parkin, T. W., Hargraves, M. M., and Odel, H. M.: Acute systemic lupus erythematosus syndrome from hydralazine hydrochloride, Arch. Int. Med. 95: 857 (June) 1955.
- Henny, F. A.: Intra-articular injection of hydrocortisone into the temporomandibular joint, J. Oral Surg. 12: 314 (Oct.) 1954.
- Henny, F. A.: The painful temporomandibular joint, J. Oral Surg. 13: 341 (Oct.) 1955.
- Hermel, M. B., and Albert, S. M.: Osteochondritis dissecans of the supratrochlear septum, J. Albert Einstein M. Center 3: 101 (May) 1955.
- 952. Hermel, M. B., and Sklaroff, D. M.: Roentgen changes in transient synovitis of the hip joint, Arch. Surg. 68: 364 (Mar.) 1954.
- 953. Hernaman-Johnson, F.: Prognosis of spondylitis in relation to treatment, Brit. J. Radiol. 18: 306 (Oct.) 1945.
- 954. Hershkowitz, M.: Fourteen months of continuous Butazolidin therapy in a seventy-three-year-old woman, New York State J. Med. 55: 1627 (June 1) 1955.
- 955. Heyman, J.: Role of the general practitioner in arthritis and rheumatic diseases, J. M. Soc. New Jersey 52: 559 (Nov.) 1955.
- 956. Hicks, A. R. H.: A case of acromegalic arthropathy, Ann. Phys. Med. 2: 299 (Oct.) 1955.
- 957. Hicks, J. D.: Synovial sarcoma of the tibia, J. Path. and Bact. 67: 151 (Jan.) 1954.
- Hidvégi, E., and Kelentei, B.: Increasing the permeability to antibiotics of the synovial barrier, Acta Physiol. Acad. Sc. Hung. 5: 521, 1954.

- 959. Hidvégi, E.: On the finer structure and blood supply of the synovial membrane, with special regard to its physiological circulation, Acta Morphol. Hung. 4: 319, 1954.
- 960. Highsmith, L. S.: Surgical non-bony lesions about the wrist, West. J. Surg. 62: 431 (Aug.) 1954.
- Highton, T. C.: A clinical trial of a derivative of a bile salt in the treatment of rheumatoid arthritis, a preliminary communication, New Zealand M. J. 53: 569 (Dec.) 1954.
- 962. Higley, G. B., Ray, R. B., Minear, W. L., and Addison, R. G.: Surgical treatment of bone and joint tuberculosis combined with streptomycin therapy, South. M. J. 47: 584 (June) 1954.
- 963. Hill, D. F.: Basic treatment in rheumatoid arthritis, M. Clin. North America 39: 393 (Mar.) 1955.
- Hill, E. J.: Skin grafting in periarteritis nodosa, Plast. and Reconstruct. Surg. 15: 186 (Mar.) 1955.
- 965. Hillman, R. W., Nerb, L., and Hertz, H.: Plasma concentrations of vitamin A, carotene, and tocopherols in rheumatic fever during ACTH therapy, New York State J. Med. 55: 2787 (Oct. 1) 1955.
- Hilton, G.: X-ray treatment of ankylosing spondylitis, Rheumatism 11: 10 (Jan.) 1955.
- Hinds, E. C., and Degnan, E. J.: The use of Achromycin and neomycin in the treatment of actinomycosis, Oral Surg., Oral Med. and Oral Path. 8: 1034 (Oct.) 1955.
- Hines, R. A.: Peripheral neuritis following isoniazid therapy, appearance of Dupuytren's contracture and Raynaud's phenomenon, J. A. M. A. 169: 1197 (Nov. 19) 1955.
- Hirsch, C., and Nachemson, A.: New observations on the mechanical behavior of lumbar discs, Acta orthop. Scandinav. 23: 254, 1954.
- 970. Hirsch, C.: The reaction of intervertebral discs to compression forces, J. Bone and Joint Surg. 37A: 1188 (Dec.) 1955.
- Hirschowitz, B. I., Streeten, D. H. P., Pollard, H. M., and Boldt, H. A., Jr.: Role of gastric secretions in activation of peptic ulcers by corticotropin (ACTH), J. A. M. A. 158: 27 (May 7) 1955.
- 972. Hjorth, N.: Felty's syndrome with ulcer of the leg, report of a case treated with corticotropin, Acta dermat.-venereol. 34: 69, 1954.
- 973. Hoffman, W. S.: Metabolism of uric acid and its relation to gout, J. A. M. A. 154: 213 (Jan. 16) 1954.
- 974. Hoffman, W. S.: Modern advances in the management of gout, M. Clin. North America 39: 307 (Jan.) 1955.
- 975. Holbrook, W. P.: Cortisone, ACTH and phenylbutazone in long-term therapy of rheumatoid arthritis, M. Clin. North America 39: 405 (Mar.) 1955.
- 976. Holden, N. T.: Deposition of calcium salts in the popliteus tendon, J. Bone and Joint Surg. 37B: 446 (Aug.) 1955.
- 977. Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., Udell, L., Smukler, N. M., and Bowie, M. A.: Hydrocortisone tertiary-butyl-acetate by intra-articular injection, J. A. M. A. 158: 476 (June 11) 1955.
- Hollander, J. L., Brown, E. M., Jr., and Jessar, R. A.: Intra-articular hydrocortisone in the management of rheumatic diseases, M. Clin. North America 38: 349 (Mar.) 1954.
- Hollander, J. L., Brown, E. M., Jr., Jessar, R. A., Udell, L., Smukler, N., and Bowie, M. A.: Local anti-rheumatic effectiveness of higher esters and analogues of hydrocortisone, Ann. Rheumat. Dis. 13: 297 (Dec.) 1954.
- Hollander, J. L.: Prednisone and prednisolone: newest corticosteroids, Merck Rep. 64: 3 (Oct.) 1955.

- Hollander, J. L.: The use of intra-articular hydrocortisone, its analogs, and its higher esters in arthritis, Ann. New York Acad. Sc. 61: 511 (May 27) 1955.
- 982. Holley, H. L.: Research in arthritis, J. M. A. Alabama 24: 157 (Jan.) 1955.
- 983. Holopainen, T., and Koskinen, H.: The effect of intravenous calcium gluconate infusion on the calcium and phosphorus excretion of patients with rheumatoid arthritis, Acta Rheum. Scandinav. 1: 250, 1955.
- 984. Holopainen, T. E., and Koskinen, H. M.: Serum precipitation test in rheumatoid arthritis according to Jokinen, Ann. med. exper. et biol. Fenniae 32: 419, 1954.
- 985. Holt, K. S., Illingworth, R. S., Lorber, J., and Rendle-Short, J.: Cortisone and salicylates in rheumatic fever, Lancet 2: 1144 (Dec. 4) 1954.
- 986. Holt, K. S.: Salicylates in rheumatic fever, difficulties experienced in treating children with large doses, Lancet 2: 1197 (Dec. 11) 1954.
- 987. Horner, D. B.: Chondromalacia of the patella, Journal Lancet 75: 365 (Sept.) 1955.
- 988. Horrax, G., and Price, W. T., Jr.: High cervical chordotomy for relief of intractable pain in the arm, shoulder and upper chest, Ann. Surg. 139: 567 (May) 1954.
- Horwitz, N. H., Whitcomb, B. B., and Reilly, F. G.: Ruptured thoracic discs, Yale J. Biol. and Med. 28: 322 (Dec.) 1955.
- 990. Houser, H. B., Clark, E. J., and Stolzer, B. L.: Comparative effects of aspirin, ACTH and cortisone on the acute course of rheumatic fever in young adult males, Am. J. Med. 16: 168 (Feb.) 1954.
- Howard, L. D., Jr.: Surgical treatment of rheumatic tenosynovitis, Am. J. Surg. 89: 1163 (June) 1955.
- 992. Howell, R. G.: Sarcoidosis with involvement of the central nervous system, Proc. Roy. Soc. Med. 47: 1065 (Dec.) 1954.
- 993. Howell, T. H.: Prolonged action of local anaesthetics in rheumatic disease, Brit. J. Phys. Med. 17: 159 (July) 1954.
- 994. Howell, T. H.: Relief of rheumatic pains with diethylamine salicylate cream: a clinical trial, Brit. J. Phys. Med. 18: 62 (Mar.) 1955.
- 995. Hrenoff, A. K.: Erythema nodosum treated with cortisone and complicated by tuberculous adenitis, Postgrad. Med. 15: 139 (Feb.) 1954.
- 996. Huff, S. E.: Observations on peripheral circulation in various dermatoses, Arch. Dermat. and Syph. 71: 575 (May) 1955.
- 997. Huffman, E. R., Wilson, G. M., Smyth, C. J., and Hill, R.: Metabolic effect of phenylbutazone in gouty and non-gouty arthritis, Ann. Rheumat. Dis. 13: 317 (Dec.) 1954.
- 998. Hult, L.: Cervical, dorsal and lumbar spinal syndromes, a field investigation of a non-selected material of 1200 workers in different occupations with special reference to disc degeneration and so-called muscular rheumatism, Acta orthop. Scandinav. Supp. 17, 1954.
- 999. Hult, L.: The Munkfors investigation, a study of the frequency and causes of the stiff neck-brachialgia and lumbago-sciatica syndromes, as well as observations on certain signs and symptoms from the dorsal spine and the joints of the extremities in industrial and forest workers, Acta orthop. Scandinav. Supp. 16, 1954.
- 1000. Hunt, T. E., and Trew, J. A.: Zone electrophoretic studies of plasma proteins in rheumatoid arthritis and ankylosing spondylitis, Ann. Rheumat. Dis. 13: 201 (Sept.) 1954.
- 1001. Hurlburt, F. W. B., and Robinson, C. E. G.: Long-term cortisone therapy in rheumatoid arthritis, Canad. M. A. J. 70: 645 (June) 1954.
- 1002. Hursh, L. M.: Arthritis following use of desoxycorticosterone acetate and cortisone, occurrence in patient with adrenal cortical hypofunction, J. A. M. A. 157: 1005 (Mar. 19) 1955.
- 1003. Hutchison, H. E., and Alexander, W. D.: Splenic neutropenia in the Felty syndrome, Blood 9: 986 (Oct.) 1954.

- 1004. Illingworth, R. S., Burke, J., Doxiadis, S. A., Lorber, J., Philpott, M. G., and Stone, D. G. H.: Salicylates in rheumatic fever: an attempt to assess their value, Quart. J. Med. 23: 177 (Apr.) 1954.
- 1005. Irving, E. A., and Tomlin, S. G.: Collagen, reticulum and their argyrophilic properties. Proc. Rov. Soc., London S. B 142: 113 (Feb.) 1954.
- 1006. Irving, J., and Le Brun, H.: Myositis ossificans in hemiplegia, J. Bone and Joint Surg. 36B: 440 (Aug.) 1954.
- 1007. Isaacson, N. H., and McCarty, D.: Recurring myxomatous cutaneous cyst, Surgery 35: 621 (Apr.) 1954.
- 1008. Ishmael, W. K.: The problem of the painful spine, J. Oklahoma M. A. 48: 375 (Nov.) 1955.
- 1009. Israel, H. L., Sones, M., and Harrell, D. D.: Cortisone treatment of sarcoidosis, Internat. Rec. Med. 168: 88 (Feb.) 1955.
- 1010. Israel, H. L., Sones, M., and Harrell, D.: Cortisone treatment of sarcoidosis, experience with thirty-six cases, J. A. M. A. 156: 461 (Oct. 2) 1954.
- 1011. Israel, H. L., and Sones, M.: The diagnosis of sarcoidosis with special reference to the Kveim reaction, Ann. Int. Med. 43: 1269 (Dec.) 1955.
- 1012. Ivins, J. C.: Disease in the entire hip joint: septic arthritis, "osteoarthritis" and traumatic dislocation of the hip, Proc. Staff Meet., Mayo Clin. 29: 43 (Jan. 27) 1954.
- 1013. Jackson, A.: Amyloidosis; report of three cases with some considerations as to etiology and pathogenesis, Arch. Int. Med. 93: 494 (Apr.) 1954.
- 1014. Jackson, D. S., and Kellgren, J. H.: Hyaluronic acid in Heberden's nodes, Ann. Rheumat. Dis. 16: 238 (June) 1957.
- 1015. Jackson, D. S.: The nature of collagen-chondroitin sulphate linkages in tendon, Biochem. J. 56: 699 (Apr.) 1954.
- 1016. Jackson, R.: The cervical syndrome, Clin. Orthop. 5: 138, 1955.
- 1017. Jackson, S. F.: Fibrogenesis in connective tissues, Nature, London 173: 950 (May 15) 1954.
- 1018. Jackson, S. F.: The formation of connective and skeletal tissues, Proc. Roy. Soc. London S. B 142: 536 (Sept.) 1954.
- 1019. Jackson, W. M., Sigler, J. W., Ensign, D. C., Fleming, J. L., and Long, C.: Rehabilitation in arthritis, J. Michigan M. Soc. 54: 330 (Mar.) 1955.
- 1020. Jackson, W. P. U., Albright, F., Drewry, G., Hanelin, J., and Rubin, M. I.: Metaphyseal dysplasia, epiphyseal dysplasia, diaphyseal dysplasia, and related conditions. I. Familial metaphyseal and craniometaphyseal dysplasia; their relation to leontiasis ossea and osteopetrosis; disorders of "bone remodeling," Arch. Int. Med. 94: 871 (Dec.) 1954.
- 1021. Jackson, W. P. U., Hanelin, J., and Albright, F.: Metaphyseal dysplasia, epiphyseal dysplasia, diaphyseal dysplasia, and related conditions. II. Multiple epiphyseal dysplasia; its relation to other disorders of epiphyseal development, Arch. Int. Med. 94: 886 (Dec.) 1954.
- 1022. Jackson, W. P. U.: Osteoporosis—commonest of all diseases, South African M. J. 29: 885 (Sept. 17) 1955.
- 1023. Jacobs, A. G.: A false-positive lupus erythematosus test, Ann. Int. Med. 42: 1097 (May) 1955.
- 1024. Jacobs, A. L., Leitner, Z. A., Moore, T., and Sharman, I. M.: Vitamin A in rheumatic fever, J. Clin. Nutrition 2: 155 (May) 1954.
- 1025. Jacobs, J. H., and Rose, F. C.: The familial occurrence of ankylosing spondylitis, Brit. M. J. 2: 1139 (Nov. 13) 1954.
- 1026. Jacobs, J. H., and Rose, F. C.: Pneumonia occurring during ACTH and cortisone therapy, Tubercle 36: 113 (April) 1955.

- 1027. Jacox, R. F., and Feldmahn, A.: Variations of beta glucuronidase concentration in abnormal human synovial fluid, J. Clin. Investigation 34: 263 (Feb.) 1955.
- 1028. Jacques, R. H.: Non-articular rheumatism, Ohio State M. J. 50: 245 (Mar.) 1954.
- 1029. James, D. G., and Thomson, A. D.: The Kveim test in sarcoidosis, Quart. J. Med. 24: 49 (Jan.) 1955.
- 1030. Janes, J. M.: Degenerative lesions of the hip joint: disease primarily in the head of the femur, Proc. Staff Meet., Mayo Clin. 29: 34 (Jan. 27) 1954.
- 1031. Järvinen, K. A. J., and Kumlin, T.: Carcinoma of the lung simulating early rheumatoid arthritis, Ann. Rheumat. Dis. 13: 52 (Mar.) 1954.
- 1032. Järvinen, K. A. J.: Rheumatoid arthritis and arterial pressure, Acta Rheum. Scandinav. 1: 127, 1955.
- 1033. Jaschik, E.: Nursing care of the arthritic patient at home, Am. J. Nursing 55: 429 (Apr.) 1955.
- 1034. Jasmin, G., and Selye, H.: Recent studies on anaphylactoid inflammation, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 8.
- 1035. Jeeves, R. J.: Equipment for a mobile physiotherapy unit, Brit. J. Phys. Med. 18: 242 (Nov.) 1955.
- 1036. Jefferies, W. McK.: The present status of ACTH, cortisone and related steroids in clinical medicine, New England J. Med. 253: 441 (Sept. 15) 1955.
- 1037. Jeffrey, M. R., Freundlich, H. F., Jackson, E. B., and Watson, D.: The absorption and utilization of radioiron in rheumatoid disease, Clin. Sc. 14: 395 (Aug.) 1955.
- 1038. Jeffrey, M. R., and Watson, D.: Free erythrocyte porphyrin and plasma copper in rheumatoid disease, Acta hæmat. 12: 169 (Sept.) 1954.
- 1039. Jenkins, J. S.: Disseminated lupus erythematosus presenting as pneumonia, Proc. Roy. Soc. Med. 48: 755 (Sept.) 1955.
- 1040. Jennings, G. C.: Some aspects of lumbago and sciatica in general practice, New Zealand M. J. 54: 691 (Dec.) 1955.
- 1041. Jennings, G. H.: Sodium salicylate and gout, Rheumatism 10: 58 (July) 1954.
- 1042. Jensen, B.: Schönlein-Henoch's purpura, three cases with fish or penicillin as antigen, Acta med. Scandinav. 152: 61, 1955.
- 1043. Jensen, C. E., and Djurtoft, R.: Hyaluronic acid. VIII. A preliminary diffusion and sedimentation study of potassium hyaluronate including a determination of the partial specific volume, Acta chem. Scand. 8: 1659, 1954.
- 1044. Jessar, R. A., and Hollander, J. L.: Types of arthritis and their medical treatment, Am. J. Nursing 55: 426 (Apr.) 1955.
- 1045. Jessup, R., Murray, R. J., and Rossi, A.: The management of low back pain in the ambulant patient, Am. Pract. and Digest Treat. 5: 792 (Oct.) 1954.
- 1046. Jocson, C. T.: The diffusion of antibiotics through the synovial membrane, J. Bone and Joint Surg. 37A: 107 (Jan.) 1955.
- 1047. Johansmann, R. J., and Zeek, P.: Periarteritis nodosa in a week-old infant, Arch. Path. 58: 207 (Sept.) 1954.
- 1048. Johnson, B. M., and Larkin, I. M.: Phenylbutazone and renal function, Brit. M. J. 2: 1088 (Nov. 6) 1954.
- 1049. Johnson, D. A.: Posture and cervicobrachial pain syndromes, J. A. M. A. 159: 1507 (Dec. 17) 1955.
- 1050. Johnson, E. W., Jr., and Weed, L. A.: Brucellar bursitis, J. Bone and Joint Surg. 36A: 133 (Jan.) 1954.
- 1051. Johnson, G. D.: The determination of antistreptolysin, J. Clin. Path. 8: 296 (Nov.) 1955.
- 1052. Johnson, H. P., Jr., Engleman, E. P., Forsham, P. H., Krupp, M. A., Green, T. W., and Goldfien, A.: Effects of phenylbutazone in gout, New England J. Med. 250: 665 (Apr. 22) 1954.

- 1053. Johnson, J. B., Davis, T. W., and Bullock, W. H.: Bone and joint changes in hemophilia, a long-term study in twelve Negro subjects, Radiology 63: 64 (July) 1954.
- 1054. Johnson, L. G., and Mackenzie, K. R.: Some metabolic observations in rheumatoid arthritis, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955.
- 1055. Johnson, N. J., and Dodd, K.: Juvenile rheumatoid arthritis, M. Clin. North America 39: 459 (Mar.) 1955.
- 1056. Johnson, R. E., and Hall, A. P.: Rubella arthritis, report of cases studied by latex tests, New England J. Med. 258: 743 (Apr. 10) 1958.
- 1057. Johnston, J. P.: A comparison of the properties of hyaluronic acid from normal and pathological human synovial fluids, Biochem. J. 59: 626 (Apr.) 1955.
- 1058. Johnston, J. P.: The sedimentation behavior of mixtures of hyaluronic acid and albumin in the ultracentrifuge, Biochem. J. 59: 620 (Apr.) 1955.
- 1059. Johnston, J. P.: The viscosity of normal and pathological human synovial fluids, Biochem. J. 59: 633 (Apr.) 1955.
- 1060. Jones, A. C.: Clinical observations in the use of ultrasonics, Am. J. Phys. Med. 33: 46 (Feb.) 1954.
- 1061. Jones, G. B.: Acute episodes with calcification around the hip joint, J. Bone and Joint Surg. 37B: 448 (Aug.) 1955.
- 1062. Jones, O. W., Jr.: The lumbar intervertebral disk problem, Indust. Med. 23: 112 (Mar.) 1954.
- 1063. Jones, R. S., and Carter, Y.: Incorporation in adrenal cortex of C¹⁶ labeled fractions of Klebsiella pneumoniae, Proc. Soc. Exper. Biol. and Med. 90: 148 (Oct.) 1955.
- 1064. Jones, R. S., Carter, Y., and Rankin, J. de W.: Rheumatic-like lesions in the guineapig: a correlation of toxic, anaphylactogenic, arthropathic and chemical properties of certain crude polysaccharides from *Klebsiella pneumoniae* type B, Brit. J. Exper. Path. 35: 519 (Dec.) 1954.
- 1065. Jones, R. S., and Carter, Y.: A study of the pathogenesis of rheumatic-like lesions in the guinea pig, Arch. Path. 58: 613 (Dec.) 1954.
- 1066. Jones, T. D.: Diagnosis and management of rheumatic fever, Heart Bull. 3: 112 (Nov.) 1954.
- 1067. Jones, T. D., Chairman: Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infections, Circulation 11: 317 (Feb.) 1955.
- 1068. Jørgensen, S., and Poulsen, H. E.: On accumulation of hypoxanthine plus xanthine in withdrawn human blood, Acta pharmacol. et toxicol. 11: 287, 1955.
- 1069. Jørgensen, S., and Poulsen, H. E.: Enzymic determination of hypoxanthine and xanthine in human plasma and urine, Acta pharmacol. et toxicol. 11: 223, 1955.
- 1070. Jørgensen, S.: Hypoxanthine and xanthine accumulated in stored human blood: determination of the relative amounts by spectrophotometry, Acta pharmacol. et toxicol. 11: 265, 1955.
- 1071. Josephs, C.: Observations on the treatment of rheumatoid arthritis by transfusions of blood from pregnant women, Brit. M. J. 2: 134 (July 17) 1954.
- 1072. Joske, R. A., and King, W. E.: The "L. E. cell" phenomenon in active chronic viral hepatitis, Lancet 2: 477 (Sept. 3) 1955.
- 1073. Josselyn, I. M., Simon, A. J., and Eells, E.: Anxiety in children convalescing from rheumatic fever, Am. J. Orthopsychiat. 25: 109 (Jan.) 1955.
- 1074. Judet, J.: The direct surgical attack on focal lesions in tuberculosis of the bones, in Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 109.
- 1075. Judovich, B. D., and Nobel, G. R.: Herniated cervical disk and atypical facial neuralgia, muscle spasm as a pain factor, Journal Lancet 75: 453 (Oct.) 1955.

- 1076. Judovich, B. D., and Nobel, G. R.: Pain problems of the neck, shoulder girdle, and upper extremity, Journal Lancet 74: 266 (July) 1954.
- 1077. Junkersdorf, J.: Rheumatism and acromegalic arthrosis, Rheumatism 11: 8 (Jan.) 1955.
- 1078. Kalliomäki, L.: Correlation of the erythrocyte sedimentation rate and gold complications in rheumatoid arthritis, Ann. Rheumat. Dis. 13: 336 (Dec.) 1954.
- 1079. Kalliomäki, L.: The histamine-eosinophil test in rheumatoid arthritis and rheumatic fever, Acta Rheum. Scandinav. 1: 235, 1955.
- 1080. Kalliomäki, L., and Kasanen, A.: The potassium and sodium contents of the serum in rheumatoid arthritis, Ann. med. int. Fenniae 44: 141, 1955.
- 1081. Kalliomäki, L.: Role of various surgical operations in the history of patients with rheumatoid arthritis, Ann. Rheumat. Dis. 13: 341 (Dec.) 1954.
- 1082. Kalliomäki, L.: Therapy of rheumatic fever, comparison of results obtained with salicylates, cortisone or corticotrophin, phenylbutazone, and combination of sodium salicylate, para-aminobenzoic acid and cortisone, Acta med. Scandinav. 152: 473, 1955.
- 1083. Kammerling, E. M., and Turner, S. J.: Subacute disseminated lupus erythematosus and uneventful pregnancy, J. Internat. Coll. Surgeons 22: 204 (Aug.) 1954.
- 1084. Kane, C. A., and Lane, G. M.: The diagnosis and management of herniated disks, M. Clin. North America 39: 1463 (Sept.) 1955.
- 1085. Kaplan, A.: Neurilemmoma of the cauda equina in a patient with spondylolisthesis, Bull. Hosp. Joint Dis. 16: 54 (Apr.) 1955.
- 1086. Kaplan, I. W., and Tyler, L. T.: Diagnosis and treatment of the painful shoulder, J. Louisiana M. Soc. 106: 351 (Sept.) 1954.
- 1087. Kaplan, R.: Septic arthritis after intra-articular injection of hydrocortisone, J. A. M. A. 155: 597 (June 5) 1954.
- 1088. Kass, E. H., Hechter, O., Mou, T. W., and Lurie, M. B.: Comparative effects of corticosterone and hydrocortisone on resistance to infection, Tr. A. Am. Physicians 68: 92, 1955.
- 1089. Kass, E. H., Hechter, O., Mou, T. W., and Lurie, M.B.: Effects of adrenal steroids on resistance to infection, Arch. Int. Med. 96: 397 (Sept.) 1955.
- 1090. Kass, E. H., Kendrick, M. I., and Finland, M.: Effects of corticosterone, hydrocortisone, and corticotropin on production of antibodies in rabbits, J. Exper. Med. 102: 767 (Dec.) 1955.
- 1091. Kass, I., Jackson, A., and Slavin, M.: Sarcoidosis: a hypersensitivity disease, J. Allergy 25: 453 (Sept.) 1954.
- 1092. Kass, E. H.: Some effects of adrenocortical hormones on mechanisms of resistance to infection, Sinai Hosp. J., Balto. 3: 1 (Nov.) 1954.
- 1093. Katz, I., and Steiner, K.: Ehlers-Danlos syndrome with ectopic bone formation, Radiology 65: 352 (Sept.) 1955.
- 1094. Katz, J. F.: Protein-bound iodine in Legg-Calvé-Perthes disease, J. Bone and Joint Surg. 37A: 842 (July) 1955.
- 1095. Kay, R., Tovell, R., and Scoville, W. B.: Regional anesthesia for operative removal of ruptured cervical intervertebral disk, Anesth. and Analg. 33: 52 (Jan.-Feb.) 1954.
- 1096. Kay, S., and Royster, H. P.: The use of cortisone in the treatment of sarcoidosis of the spleen prior to splenectomy, Surgery 36: 798 (Oct.) 1954.
- 1097. Keats, T. E., and Bagnall, W. S.: Chronic idiopathic osteoarthropathy, Radiology 62: 841 (June) 1954.
- 1098. Keech, M. K.: The effect of collagenase and trypsin on collagen, Anat. Rec. 119: 139 (June) 1954.
- 1099. Keech, M. K.: The effect of collagenase on human skin collagen, comparison of different age-groups and of cases with and without "collagen disease," Yale J. Biol. and Med. 26: 295 (Feb.) 1954.

- 1100. Keech, M. K.: Human skin collagen from different age groups before and after collagenase digestion, an electron microscopic study, Ann. Rheumat. Dis. 14: 19 (Mar.) 1955.
- 1101. Keech, M. K.: The percentage of tapered fibril ends in skin collagen from cases with and without "collagen disease," Yale J. Biol. and Med. 26: 527 (June) 1954.
- 1102. Keet, P. W. J.: Sciatic and analogous root pains and their treatment by paravertebral injection, South African M. J. 28: 65 (Jan. 23) 1954.
- 1103. Kelényi, G.: Effect of cytotoxic agents on tissue mast cells, Acta Morphol. Hung. 4: 345, 1954.
- 1104. Kelényi, G.: Effect of x-ray irradiation and caryoclastic substances upon tissue mast cells, Acta Morphol. Hung. 4: 128, 1954.
- 1105. Kelleher, J., and Sneddon, I. B.: The management of psychotic reactions resulting from cortisone and corticotrophin, Practitioner 175: 300 (Sept.) 1955.
- 1106. Kellett, C. E.: Complementary activity of the blood in rheumatism and certain allied disorders, Ann. Rheumat. Dis. 13: 211 (Sept.) 1954.
- 1107. Kelley, V. C.: Rationale for hormone therapy in rheumatic fever, Ann. New York Acad. Sc. 61: 369 (May 27) 1955.
- 1108. Kelley, V. C.: The role of the pituitary-adrenal system in rheumatic fever, Journal Lancet 75: 291 (July) 1955.
- 1109. Kelley, V. C.: Studies of pituitary-adrenal hormones in children in health and disease, Pediatrics 15: 1 (Jan.) 1955.
- 1110. Kelley, V. C., Ely, R. S., Done, A. K., and Ainger, L. E.: Studies of 17-hydroxy-corticosteroids. VI. Circulating concentrations in patients with rheumatic fever, Am. J. Med. 18: 20 (Jan.) 1955.
- 1111. Kellgren, J. H.: Non-articular rheumatism, in Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 159.
- 1112. Kellgren, J. H.: Primary generalised osteoarthritis, Bull. Rheumat. Dis. 4: 46 (Jan.) 1954.
- 1113. Kellner, A., and Robertson, T.: Myocardial necrosis produced in animals by means of crystalline streptococcal proteinase, J. Exper. Med. 99: 495 (May) 1954.
- 1114. Kellner, A., and Robertson, T.: Selective necrosis of cardiac and skeletal muscle induced experimentally by means of proteolytic enzyme solutions given intravenously, J. Exper. Med. 99: 387 (Apr.) 1954.
- 1115. Kellogg, R. O.: Steroid therapy in rheumatoid arthritis, J. Maine M. A. 46: 345 (Dec.) 1955.
- 1116. Kelly, H. G., Hill, J. G., and Boyd, E. M.: The absence of cortisone therapy upon plasma lipid levels in patients with rheumatoid arthritis, Canad. M. A. J. 70: 660 (June) 1954.
- 1117. Kelly, H. G.: Gout, Canad. M. A. J. 72: 735 (May 15) 1955.
- 1118. Kelly, H. G.: The medical management of rheumatoid arthritis, Canad. M. A. J. 72: 283 (Feb. 15) 1955.
- 1119. Kelly, M.: The alleviation of rheumatic pain, Butazolidin: immobilization: procaine, Rheumatism 11: 72 (Oct.) 1955.
- 1120. Kelly, M.: Anti-rheumatic potency of Butazolidin in low doses, Brit. J. Phys. Med. 18: 191 (Sept.) 1955.
- 1121. Kelly, M.: Can pain be hysterical?, M. J. Australia 2: 891 (Nov. 26) 1955.
- 1122. Kelly, M.: Constriction pain in muscle, ischemic or neural?, Neurology 5: 178 (Mar.) 1955.
- 1123. Kelly, M.: Does reduced blood-supply cause pain?, Lancet 1: 747, 1955.
- 1124. Kelly, M.: How to prevent crippling in rheumatoid arthritis, Lancet 1: 1158 (June 5) 1954.

- 1125. Kelly, M.: The management of rheumatoid arthritis, Medicine Illus. (London) 9: 302 (May) 1955.
- 1126. Kelly, M.: Phenylbutazone (Butazolidin) and cortisone in rheumatoid arthritis, M. J. Australia 2: 592 (Oct. 8) 1955.
- 1127. Kelly, M.: Phenylbutazone ("Butazolidin"): good or evil antirheumatic or analgesic? M. J. Australia 2: 504 (Sept. 25) 1954.
- 1128. Kelly, M.: Should arthritic patients become crippled?, Australian J. Physiotherapy 1: 69 (Mar.) 1955.
- 1129. Kelly, R. P., and Johnson, J. T.: Acute low back pain, J. A. M. A. 158: 1520 (Aug. 27) 1955.
- 1130. Kempner, W., Peschel, E., and Black-Schaffer, B.: Effect of diet on experimental hypertension and on the development of polyarteritis nodosa in rats, Circul. Res. 3: 73 (Jan.) 1955.
- 1131. Kennedy, J. J.: Tubular structure of collagen fibrils, Science 121: 673 (May 6) 1955. 1132. Kerby, G. P.: The excretion of glucuronic acid and of acid mucopolysaccharides in
- 1132. Kerby, G. P.: The excretion of glucuronic acid and of acid mucopolysaccharides in normal human urine, J. Clin. Investigation 33: 1168 (Aug.) 1954.
- 1133. Kerby, G. P.: The occurrence of acid mucopolysaccharides in human leukocytes and urine, J. Clin. Investigation 34: 1738 (Dec.) 1955.
- 1134. Kerr, H. D.: Radiation treatment of nonmalignant conditions, J. Louisiana M. Soc. 107: 177 (May) 1955.
- 1135. Kersley, G. D., Barber, H. S., Cregan, J. C. F., and Gibson, H. J.: Degenerative rheumatoid changes, J. Bone and Joint Surg. 36B: 238 (May) 1954.
- 1136. Kersley, G. D.: Syndromes of rheumatoid arthritis, Lancet 1: 1206 (June 12) 1954.
 1137. Kilroy, D. O.: Hydrocortisone therapy of periarticular pain, California Med. 83: 416 (Dec.) 1955.
- 1138. King, A. B.: Back pain due to a loose lumbar facet, Arch. Neurol. and Psychiat. 74: 102 (July) 1955.
- 1139. King, A. B.: Back pain due to loose facets of the lower lumbar vertebrae, Bull. Johns Hopkins Hosp. 97: 271 (Oct.) 1955.
- 1140. King, R. E., Blalock, J. C., and Lovell, W. W.: An unusual spine lesion, possibly typhoid: report of a case, J. Bone and Joint Surg. 36A: 863 (July) 1954.
- 1141. King, S. H.: Psychosocial factors associated with rheumatoid arthritis, J. Chron. Dis. 2: 287 (Sept.) 1955.
- 1142. Kingma, M. J.: Results of arthroplasty of the hip joint, Arch. chir. Neerl. 6: 323, 1954.
- 1143. Kinsell, L. W.: Emergency and prophylactic corticoid therapy in individuals past 50, J. Am. Geriatrics Soc. 3: 285 (May) 1955.
- 1144. Kinsell, L. W.: Suppressive as compared with analgesic hormonal therapy in patients with rheumatoid arthritis, Ann. Rheumat. Dis. 13: 307 (Dec.) 1954.
- 1145. Kipnis, D. M., and Sacks, M. S.: Observations on an agglutinin in human serum for periodate-treated erythrocytes, J. Lab. and Clin. Med. 45: 632 (Apr.) 1955.
- 1146. Kirsner, J. B., and Ford, H.: Phenylbutazone (Butazolidin) effect on basal gastric secretion and the production of gastroduodenal ulcerations in dogs, Gastroenterology 29: 18 (July) 1955.
- 1147. Kirsner, J. B., and Ford, H.: Phenylbutazone (Butazolidin) studies on the stimulation of gastric secretion and the formation of peptic ulcer in man, Gastroenterology 29: 1 (July) 1955.
- 1148. Kiss, F.: Nerves of the collagen fibres, Acta Morphol. Hung. 4: 124, 1954.
- 1149. Kite, J. H.: Arthrogryposis multiplex congenita, South. M. J. 48: 1141 (Nov.) 1955.
- 1150. Kieckner, M. S., Jr., and Magidson, J.: Amyloidosis of the liver, correlation of clinical and pathologic features, Gastroenterology 29: 56 (July) 1955.
- 1151. Klein, M., Calvert, R. J., Joseph, W. E., and Smith, E.: Rarities in ocular sarcoidosis, Brit. J. Ophth. 39: 416 (July) 1955.

- 1152. Klein, R., and Harris, S. B.: Treatment of scleroderma, sclerodactylia and calcinosis by chelation (EDTA), Am. J. Med. 19: 798 (Nov.) 1955.
- 1153. Klemperer, P.: The significance of the intermediate substances of the connective tissue in human disease, Harvey Lecture 49: 100, 1953-1954.
- 1154. Knapp, M. E., and Engel, J. P.: Diagnosis and treatment of the painful shoulder, J. A. M. A. 157: 995 (Mar. 19) 1955.
- 1155. Knight, G.: Facetectomy in the treatment of cervical rhizalgia, Proc. Roy. Soc. Med. 48: 595 (Aug.) 1955.
- 1156. Knight, R. P., Jr., Kornfeld, D. S., Glaser, G. H., and Bondy, P. K.: Effects of intravenous hydrocortisone on electrolytes of serum and urine in man, J. Clin. Endocrinol. 15: 176 (Feb.) 1955.
- 1157. Kobak, D.: Some physiologic considerations of the therapeutic action on ultrasonics, Am. J. Phys. Med. 33: 21 (Feb.) 1954.
- 1158. Kodicek, E., and Loewi, G.: The uptake of (**S) sulphate by mucopolysaccharides of granulation tissue, Proc. Roy. Soc., London, S. B 144: 100 (Aug.) 1955.
- 1159. Kofman, S., Johnson, G. C., and Zimmerman, H. J.: Apparent hepatic dysfunction in lupus erythematosus, Arch. Int. Med. 95: 669 (May) 1955.
- 1160. Kornblueh, I. H., and Piersol, G. M.: The vanishing spas of Pennsylvania, Tr. Coll. Physicians of Philadelphia Series 4 21: 63 (Aug.) 1953.
- 1161. Koumans, A. K. J.: Xylocaine in arthropathia, a contribution to the conservative treatment of joint diseases, Acta med. Scandinav. 152: 285, 1955.
- 1162. Kramár, J., Meyers, V. W., and Peetz, D. J.: Correlation between capillary resistance and circulating eosinophils, J. Lab. and Clin. Med. 43: 395 (Mar.) 1954.
- 1163. Kramár, J.: Endocrine regulation of the capillary resistance, Science 119: 790 (June 4) 1954.
- 1164. Kreidberg, M. B., Dameshek, W., and Latorraca, R.: Acute vascular (Schönlein-Henoch) purpura—an immunologic disease?, New England J. Med. 253: 1014 (Dec. 8) 1955.
- 1165. Kristeller, E. L., and Emmett, R.: Housekeeping for housewives with rheumatic diseases, Rheumatism 11: 89 (Oct.) 1955.
- 1166. Krompecher, I.: Development of the connective tissue and its capacity of transformation, Acta Morphol. Hung. 4: 113, 1954.
- 1167. Kroop, I. G., Heffer, E. T., and Shackman, N. H.: An evaluation of electrophoresis in rheumatic fever, Am. Heart J. 48: 612 (Oct.) 1954.
- 1168. Kroop, I. G.: The treatment of rheumatic fever with large doses of cortisone, New York State J. Med. 54: 2699 (Oct. 1) 1954.
- 1169. Krusen, E. M.: Pain in the neck and shoulder, common causes and response to therapy, J. A. M. A. 159: 1282 (Nov. 26) 1955.
- 1170. Krusen, E. M.: Hemiplegia: with special emphasis on problems of the shoulder, South. M. J. 48: 612 (June) 1955.
- 1171. Krusen, E. M., Jr., and Krusen, U. L.: Cervical syndrome especially the tension-neck problem: clinical study of 800 cases, Arch. Phys. Med. 36: 518 (Aug.) 1955.
- 1172. Krusen, F. H.: Physical medicine and rehabilitation for chronic illness, Ohio State M. J. 50: 929 (Oct.) 1954.
- 1173. Kuhns, J. G.: Arthritic disabilities of the knee, Brit. J. Phys. Med. 18: 270 (Dec.) 1955.
- 1174. Kuhns, J. G.: Conservative orthopaedic treatment of osteoarthritis, Rheumatism 10: 85 (Oct.) 1954.
- 1175. Kuhns, J. G.: The management of arthritic disabilities of the knee, Physiotherapy Rev. 34: 510 (Oct.) 1954.
- 1176. Kuhns, J. G.: The orthopedic treatment of chronic arthritis, Missouri Med. 51: 1002 (Dec.) 1954.
- 1177. Kuhns, J. G.: Osteoarthritis in the aged, J. Am. Geriatrics Soc. 2: 519 (Aug.) 1954.

- 1178. Kuhns, W. J., and McCarty, M.: Studies of diphtheria antitoxin in rheumatic fever subjects: analysis of reactions to the Schick test and of antitoxin responses following hyperimmunization with diphtheria toxoid, J. Clin. Investigation 33: 759 (May) 1954.
- 1179. Kuhns, W. J., and Crittenden, J.: Zone electrophoresis in studies of serum proteins, protein-bound polysaccharides and serum lipids in rheumatoid disease, J. Lab. and Clin. Med. 46: 398 (Sept.) 1955.
- 1180. Kuitert, J. H.: Ultrasonic energy as an adjunct in the management of radiculitis and similar referred pain, Am. J. Phys. Med. 33: 61 (Feb.) 1954.
- 1181. Kulka, J. P., Bocking, D., Ropes, M. W., and Bauer, W.: Early joint lesions of rheumatoid arthritis, Arch. Path. 59: 129 (Feb.) 1955.
- 1182. Kulonen, E., and Telkkä, A.: Effect of adrenal steroids on synovial tissues in vitro, Ann. med. exper. et. biol. Fenniae 32: 347, 1954.
- 1183. Kulonen, E.: On soluble collagens, Acta Rheum. Scandinav. 1: 174, 1955.
- 1184. Kulonen, E., and Mäkinen, P.: An orientating study on the synovial fluid with reference to the effect of compound F, Acta Rheum. Scandinav. 1: 89, 1955.
- 1185. Kupersmith, I. H.: Value of Phytolacca in arthritis, M. Times, New York 83: 1263 (Dec.) 1955.
- 1186. Kuzell, W. C., Schaffarzick, R. W., and Naugler, W. E.: The effect of intravenous demecolcine (Colcemid) on acute gout, Arch. Int. Med. 96: 153 (Aug.) 1955.
- 1187. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Gaudin, G., Mankle, E. A., and Brown, B.: Phenylbutazone (Butazolidin) in gout, Am. J. Med. 16: 212 (Feb.) 1954.
- 1188. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Koets, P., Mankle, E. A., Brown, B., and Champlin, B.: Some observations on 520 gouty patients, J. Chron. Dis. 2: 645 (Dec.) 1955.
- 1189. Laane, C. L.: Cushing's syndrome associated with obliterative arterial disease and multiple subcutaneous nodules (Ehlers-Danlos syndrome?), Acta med. Scandinav. 148: 323, 1954.
- 1190. Lachman, E.: Osteoporosis: the potentialities and limitations of its roentgenologic diagnosis, Am. J. Roentgenol. 74: 712 (Oct.) 1955.
- 1191. LaDu, B. N., Seegmiller, J. E., Laster, L., and Zannoni, V.: Alcaptonuria and ochronotic arthritis, Bull. Rheumat. Dis. 8: 163 (May) 1958.
- 1192. LaFia, D. J.: Ruptured lumbar intervertebral disk syndrome caused by metastatic disease, Rhode Island M. J. 38: 212 (Apr.) 1955.
- 1193. Laidlaw, J. C., Dingman, J. F., Arons, W. L., Finkenstaedt, J. T., and Thorn, G. W.: Comparison of the metabolic effects of cortisone and hydrocortisone in man, Ann. New York Acad. Sc. 61: 315 (May 27) 1955.
- 1194. Laine, V. A. I., Mäkinen, P., Mäkinen, G. L., Holopainen, T., and Sairanan, E.: The clinical significance of histological amyloid in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 257, 1955.
- 1195. Laine, V. A. I.: Early diagnosis of rheumatoid arthritis (preliminary report), Acta med. Scandinav. 149: 377, 1954.
- 1196. Laine, V. A. I., Vainio, K. J., and Holopainen, T. E.: Effect of thyroidectomy in rheumatoid arthritis, Ann. Rheumat. Dis. 13: 250 (Sept.) 1954.
- 1197. Laine, V. A. I., Holopainen, T., and Koskinen, H.: Liver function tests in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 184, 1955.
- 1198. Laine, V. A. I., Holopainen, T., and Koskinen, H.: Liver function tests on rheumatoid arthritis patients showing complication associated with gold therapy, Acta Rheum. Scandinav. 1: 196, 1955.
- 1199. Laine, V. A. I., Vainio, K., and Ritama, V. V.: Occurrence of amyloid in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 43, 1955.

- 1200. Laine, V. A. I., Vainio, K. J., and Pekanmäki, K.: Shoulder affections in rheumatoid arthritis, Ann. Rheumat. Dis. 13: 157 (June) 1954.
- 1201. Laine, V. A. I., and Vainio, K. J.: Spontaneous ruptures of tendons in rheumatoid arthritis, Acta orthop. Scandinav. 24: 250, 1955.
- 1202. Laine, V. A. I., and Vainio, K. J.: Ulceration of the skin in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 113. 1955.
- 1203. Lamb, D. W.: Localised osteochondritis of the lumbar spine, J. Bone and Joint Surg. 36B: 591 (Nov.) 1954.
- 1204. Lambert, E. H., Sayre, G. P., and Eaton, L. M.: Electrical activity of muscle in polymyositis, Tr. Am. Neurol. A. 79: 64, 1954.
- 1205. Lame, E. L., and Chang, H. C.: Pubic and ischial necrosis following cystostomy and prostatectomy (osteitis pubis), Am. J. Roentgenol. 71: 193 (Feb.) 1954.
- 1206. Lamont-Havers, R. W.: Nature of serum factors causing agglutination of sensitized sheep cells and group A hemolytic streptococci, Proc. Soc. Exper. Biol. and Med. 88: 35 (Jan.) 1955.
- 1207. Landells, J. W.: The bone cysts of osteoarthritis, J. Bone and Joint Surg. 35B: 643 (Nov.) 1953.
- 1208. Landing, B. H., and Feriozi, D.: Effect of ACTH on the adrenals in the nephrotic syndrome and rheumatic fever, J. Clin. Endocrinol. 14: 1023 (Sept.) 1954.
- 1209. Landry, W. J., Jr., Brierre, J. T., and Hunt, N. S.: Radiological evaluation of low back pain, J. Louisiana M. Soc. 107: 484 (Dec.) 1955.
- 1210. Lang, E. F., Jr.: Syndrome of median nerve compressions in carpal tunnel, S. Clin. North America 34: 853 (June) 1954.
- 1211. Langenskiöld, A.: Can osteochondritis dissecans arise as a sequel of cartilage fracture in early childhood?, Acta chir. Scandinav. 109: 206, 1955.
- 1212. Langston, R. G., and Cowan, R. J.: Dupuytren's contracture, a survey of cases five years after operation, J. Internat. Coll. Surgeons 23: 710 (June) 1955.
- 1213. Lannin, D. R.: Intervertebral disc lesions in the teenage group, Minnesota Med. 37: 136 (Feb.) 1954.
- 1214. Lansbury, J.: Collagen disease complicating malignancy, Ann. Rheumat. Dis. 12: 301 (Dec.) 1953.
- 1215. Lansbury, J., Allen, G. E., and Rogers, F. B.: Failure of skin testing to detect antigenantibody properties in the tissues of rheumatoid arthritis, Am. J. M. Sc. 229: 191 (Feb.) 1955.
- 1216. Lansbury, J., and Rogers, F. B.: The hydralazine syndrome, Bull. Rheumat. Dis. 5: 85 (Mar.) 1955.
- 1217. Lara, J. Y.: Therapeutic considerations in steroid therapy complicated by emotional disorders, Texas Rep. Biol. and Med. 12: 300, 1954.
- 1218. Laragh, J. J.: Some effects of chlorothiazide on electrolyte metabolism and its use in edematous states, Ann. New York Acad. Med. 71: 409 (Feb.) 1958.
- 1219. Laszlo, M. H., Alvarez, A., and Feldman, F.: The association of thrombotic thrombocytopenic purpura and disseminated lupus erythematosus: report of a case, Ann. Int. Med. 42: 1308 (June) 1955.
- 1220. Laurent, T. C., and Gergely, J.: Light scattering studies on hyaluronic acid, J. Biol. Chem. 212: 325 (Jan.) 1955.
- 1221. Law, W. A.: Inflammation of the subacromial bursa, Rheumatism 10: 9 (Jan.) 1954.
- 1222. Lawrence, J. S.: Rheumatism in coal miners. III. Occupational factors, Brit. J. Indust. Med. 12: 249 (Apr.) 1955.
- 1223. Lawrence, J. S., and Sladden, R. J.: The value of physiotherapy in rheumatic diseases. I. Palliation, Ann. Phys. Med. 2: 282 (Oct.) 1955.
- 1224. Lawrie, T. D. V.: Polyarteritis nodosa, report of two cases presenting with abdominal symptoms and signs, Glasgow M. J. 36: 220 (July) 1955.

- 1225. Lecce, J. G., Sperling, F: G., Hayflick, L., and Stinebring, W.: Tendovaginitis with arthritis, a new syndrome of chickens: isolation and characterization of an infectious agent, J. Exper. Med. 102: 489 (Oct.) 1955.
- 1226. Lederer, H., and Sinclair, A. J.: Malignant synovioma simulating "adamantinoma of the tibia." J. Path. and Bact. 67: 163 (Jan.) 1954.
- 1227. Lee, S. L., Schwartz, L. I., and Pariser, S.: Blood coagulation and the L. E. cell phenomenon. Blood 9: 965 (Oct.) 1954.
- 1228. Lee, S. L.: Clinical experiences with the L. E. cell test, J. Mt. Sinai Hosp. 22: 74 (July) 1955.
- 1229. Lee, S. L., Sanders, M., and Kahny, H. M.: A disorder of blood coagulation in systemic lupus erythematosus, J. Clin. Investigation 34: 1814 (Dec.) 1955.
- 1230. Lee, S. L.: Interactions of quinacrine HCl and the LE cell factor upon leukocytes, Clin. Res. Proc. 3: 98 (Apr.) 1955.
- 1231. Leese, W. L. B.: Prolonged treatment of the Schönlein-Henoch syndrome with corticotrophin, Lancet 2: 851 (Oct. 22) 1955.
- 1232. Lefkovits, A. M., and Farrow, I. J.: The liver in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 162 (June) 1955.
- 1233. Lehmann, J. F., Erickson, D. J., Martin, G. M., and Krusen, F. H.: Comparison of ultrasonic and microwave diathermy in the physical treatment of periarthritis of the shoulder, Arch. Phys. Med. 35: 627 (Oct.) 1954.
- 1234. Lehmann, J. F., Erickson, D. J., Martin, G. M., and Krusen, F. H.: Present value of ultrasonic diathermy, J. A. M. A. 157: 996 (Mar. 19) 1955.
- 1235. Leichtentritt, K. G.: Prevention of shoulder-hand syndrome, GP 12: 108 (Sept.) 1955.
- 1236. Leifer, P., and Batterman, R. C.: Local cutaneous response of nicotinic acid and esters as diagnostic aid for rheumatoid arthritis, Am. J. M. Sc. 230: 657 (Dec.) 1955.
- 1237. Leikola, E., and Vartia, K. O.: Lupus erythematosus disseminatus, Acta Rheum. Scandinav. 1: 73, 1955.
- 1238. Leinwand, I., Duryee, A. W., and Richter, M. N.: Scleroderma (based on a study of over 150 cases), Ann. Int. Med. 41: 1003 (Nov.) 1954.
- 1239. Leitch, O. W.: Denervation in osteoarthritis, M. J. Australia 2: 629 (Oct. 5) 1955.
- 1240. Leitch, O. W.: Denervation of the knee joint, Australian and New Zealand J. Surg. 24: 310 (May) 1955.
- 1241. Leitch, O. W.: The first lumbar root syndrome, M. J. Australia 2: 842 (Nov. 19) 1955.
- 1242. Lemon, H. M., Looney, J. M., and Chasen, W. H.: Glycine metabolism in rheumatoid arthritis and allied disease, Rheumatism 11: 48 (July) 1955.
- 1243. Leon, J.: The incidence and diagnosis of brucellosis, Delaware State M. J. 27: 290 (Nov.) 1955.
- 1244. Lessner, H. E., and Rose, J. C.: Primary pneumococcal arthritis of the hip, M. Ann. District of Columbia 24: 394 (Aug.) 1955.
- 1245. Lesson, G.: Origin and history of mobile physiotherapy services, Brit. J. Phys. Med. 18: 239 (Nov.) 1955.
- 1246. Levin, M. E., and Daughaday, W. H.: Tissue binding of hydrocortisone, J. Lab. and Clin. Med. 44: 829 (Nov.) 1954.
- 1247. Levin, M. E., Daughaday, W. H., and Bremer, R.: Tissue binding of hydrocortisone, J. Lab. and Clin. Med. 45: 833 (June) 1955.
- 1248. Levin, M. H., Rivo, J. B., Scott, W., Figuero, W. G., Fred, L., and Barrett, T. F.: The prolonged treatment of rheumatoid arthritis with cortisone and corticotropin, Am. J. Med. 14: 265 (Mar.) 1953.
- 1249. Levy, E. S., and Cohen, D. B.: Systemic moniliasis and aspergillosis complicating corticotropin therapy, Arch. Int. Med. 95: 118 (Jan.) 1955.

- 1250. Levy, R. I.: Psychogenic musculoskeletal reactions, M. Bull. U. S. Army, Europe 12: 175 (July) 1955.
- 1251. Lewi, S.: Rouleaux formation intensity of plasma and E. S. R., Brit. M. J. 2: 336 (Aug. 7) 1954.
- 1252. Lewis, A., and Fleminger, J. J.: The psychiatric risk from corticotrophin and cortisone, Lancet 1: 383 (Feb. 20) 1954.
- 1253. Lewis, B. I., Sinton, D. W., and Knott, J. R.: Central nervous system involvement in disorders of collagen, Arch. Int. Med. 93: 315 (Mar.) 1954.
- 1254. Lewis, B. S.: Hodgkin's disease presenting as hydrarthrosis of knee, Brit. M. J. 2: 27 (July 2) 1955.
- 1255. Lewis, G. W.: Polyarthritis in rubella, Rheumatism 10: 66 (July) 1954.
- 1256. Lewis, I. C.: The Schönlein-Henoch syndrome (anaphylactoid purpura) compared with certain features of nephritis and rheumatism, Arch. Dis. Childhood 30: 212 (June) 1955.
- 1257. Lewitus, Z.: Palindromic rheumatism with special reference to the therapeutic results with gold and ACTH, Rheumatism 10: 70 (July) 1954.
- 1258. Ley, E. B., and Thurston, W. D.: Avulsed lumbodorsal aponeurosis and low back pain, Rocky Mountain M. J. 51: 18 (Jan.) 1954.
- 1259. Ley, E. B., and Thurston, W. D.: Retroperitoneal approach to lumbar disc, Rocky Mountain M. J. 51; 121 (Feb.) 1954.
- 1260. Liban, E., Shamir, Z., and Schorr, S.: Periarteritis nodosa in a nine-month-old infant, Am. J. Dis. Child. 88: 210 (Aug.) 1954.
- 1261. Liberson, M., and Brouwer, J.: Dangers of cortisone therapy in pulmonary lesions of uncertain etiology, Connecticut M. J. 19: 727 (Sept.) 1955.
- 1262. Librach, I. M.: Erythema multiforme bullosa (Stevens-Johnson syndrome): some observations on pathogenesis and on treatment with cortisone and ACTH, Post-Grad. M. J. 31: 570 (Nov.) 1955.
- 1263. Libretti, A., Kaplan, M. A., and Goldin, M.: Precipitin analysis of C-reactive protein by gel diffusion, Proc. Soc. Exper. Biol. and Med. 90: 481 (Nov.) 1955.
- 1264. Lichtenstein, L., and Kaplan, L.: Hereditary ochronosis: pathologic changes observed in two necropsied cases, Am. J. Path. 30: 99 (Jan.) 1954.
- 1265. Lichtenstein, L.: Tumors of synovial joints, bursae, and tendon sheaths, Cancer 8: 816 (July) 1955.
- 1266. Liddle, G. W., Pechet, M. M., and Bartter, F. C.: Enhancement of biological activities of corticosteroids by substitution of halogen atoms in 9a position, Science 120: 496 (Sept. 24) 1954.
- 1267. Lieberman, A.: A psoriatic rheumatoid arthritic: successful result with massive cortisone therapy, Illinois M. J. 107: 89 (Feb.) 1955.
- 1268. Lightbody, J. J.: Foundation stimulates research in arthritis, J. Michigan M. Soc. 54: 265 (Mar.) 1955.
- 1269. Liljestrand, A., and Olhagen, B.: I. Persistently high erythrocyte sedimentation rate, diagnostic and prognostic aspects, Acta med. Scandinav. 151: 425, 1955.
- 1270. Lincoln, M.: Are we missing the diagnosis of periarteritis nodosa?, Northwest Med. 53: 1224 (Dec.) 1954.
- 1271. Linden, I. H., Laden, E., Erickson, J. O., and Armen, D.: Electron microscopic study of normal skin collagen and elastic fibers, J. Invest. Dermat. 24: 83 (Feb.) 1955.
- 1272. Lindholm, R. V.: Tissue therapy in osteoarthritis. Ann. chir. et gynaec. Fenniae 43 Supp. 5: 214, 1954.
- 1273. Link, R. P., and St. Clair, L. E.: Some metabolic studies on hypophysectomized pigs, Endocrinology 54: 290 (Mar.) 1954.
- 1274. Lintz, R. M.: Implantation of placental tissue in patients with rheumatoid arthritis, Ann. Rheumat. Dis. 13: 63 (Mar.) 1954.
- 1275. Lintz, R. M.: Placental tissue implantation for rheumatoid arthritis, a preliminary report, Geriatrics 9: 106 (Mar.) 1954.

1276. Lipkin, E.: Rheumatology, 1954: a therapeutic survey with review of cases treated with procaine hydrochloride, J. Michigan M. Soc. 54: 304 (Mar.) 1955.

1277. Lipow, E. G.: Whiplash injuries, South. M. J. 48: 1304 (Dec.) 1955.

1278. Lippman, E. M., and Grow, J. L.: Neurogenic arthropathy associated with diabetes mellitus, J. Bone and Joint Surg. 37A: 971 (Oct.) 1955.

1279. Lipschutz, A.: Morquio's disease, J. Pediat. 46: 403 (Apr.) 1955.

1280. Lipsett, M. B., and Goldman, R.: Phenylbutazone toxicity: report of a case of acute renal failure, Ann. Int. Med. 41: 1075 (Nov.) 1954.

1281. Lipton, E. L., and Morgenstern, S. H.: Arthrogryposis multiplex congenita in identical twins, Am. J. Dis. Child. 89: 233 (Feb.) 1955.

1282. Lister, L. M., and Baker, R. D.: Needle biopsy of the kidney in the diagnosis of disseminated lupus erythematosus, Am. J. Med. 17: 851 (Dec.) 1954.

1283. Lloyd-Roberts, G. C.: Osteoarthritis, Post-Grad. M. J. 31: 618 (Dec.) 1955.

1284. Lloyd-Roberts, G. C.: Osteoarthritis of the hip, a study of the clinical pathology, J. Bone and Joint Surg. 37B: 8 (Feb.) 1955.

1285. Lockhart, J. D., and Burke, F. G.: Myositis ossificans progressiva: report of a case treated with corticotropin (ACTH), Am. J. Dis. Child. 87: 626 (May) 1954.

Lockie, L. M.: Present-day treatment of gout, Bull. Rheumat. Dis. 6: 97 (Nov.) 1955.
 Loeven, W. A.: The binding collagen-mucopolysaccharide in connective tissue, Acta anat. 24: 217, 1955.

1288. Loeven, W. A.: Effect of alkali treatment of collagen on the pH-swelling curve of collagen and of gelatin products prepared from it, J. Soc. Leather Trades' Chemists 38: 117, 1954.

1289. Loeven, W. A.: The nature of the complex binding between collagen and mucopoly-saccharide in connective tissue, Acta physiol. et pharmacol. neerl. 4: 243, 1955.

1290. Lövgren, O., Norman, A., and Winqvist, G.: Inhibitory effect of vitamin B₁₂ on cortisone and ACTH, Acta Rheum. Scandinav. 1: 106, 1955.

1291. Lövgren, O., and Orström, A.: Tissue analyses with radioactive phosphorus in rheumatic arthritis, Rheumatism 10: 41 (Apr.) 1954.

1292. London, P. S.: Synovectomy of the knee in rheumatoid arthritis, J. Bone and Joint Surg. 37B: 392 (Aug.) 1955.

1293. Long, D. A.: The pathogenesis of rheumatic fever, Lancet 1: 529 (Mar. 13) 1954.

1294. Long, D. A.: Possible mechanisms of the therapeutic action of cortisone, Internat. Arch. Allergy 6: 337, 1955.

1295. Long, D. A.: Rheumatic fever as a collagen disease, Ann. Rheumat. Dis. 13: 324 (Dec.) 1954.

1296. LoPresti, J. M., and Nestor, J. O.: Prophylaxis in rheumatic fever, Clin. Proc. Child. Hosp. 11: 32 (Feb.) 1955.

1297. Lord, J. W., Jr.: Diagnostic and surgical aspects of the shoulder girdle syndromes, New York State J. Med. 55: 2021 (July 15) 1955.

1298. Losner, S., Volk, B. W., and Kanof, A.: The clot density determination of fibrinogen in rheumatic fever, Am. Heart J. 50: 100 (July) 1955.

1299. Losner, S., and Volk, B. W.: The fibrinogen polymerization test in active rheumatic disease, Am. J. M. Sc. 229: 371 (Apr.) 1955.

1300. Lous, P., and Sylvest, O.: A comparison of three methods, utilizing different principles, for the determination of uric acid in biological fluids. Scandinav. J. Clin. and Lab. Invest. 6: 40, 1954.

1301. Loutzenheiser, J. J.: Surgery of osteoarthritis, J. A. M. A. 157: 491 (Feb. 5) 1955.

1302. Louw, A.: Psycho-pathological conditions in disturbances of the function of the suprarenal cortex, Acta med. Scandinav. 151: 333, 1955.

1303. Love, J. G.: Median neuritis or carpal tunnel syndrome, North Carolina M. J. 16: 463 (Oct.) 1955.

1304. Lovell, R. R. H., and Rose, G. A.: The symptoms, diagnosis and treatment of polyarteritis, Post-Grad. M. J. 31: 382 (Aug.) 1955.

- 1305. Lowenstein, P. S., and Heeb, M. A.: Intestinal obstruction secondary to periarteritis nodosa, Angiology 6: 417 (Oct.) 1955.
- 1306. Lowman, E. W., and Lee, P. R.: The chronic rheumatoid cripple: rehabilitation assets and deficits, Bull. Rheumat. Dis. 4: 50 (Mar.) 1954.
- 1307. Lowman, E. W.: Osteoarthritis, J. A. M. A. 157: 487 (Feb. 5) 1955.
- 1308. Lowman, E. W.: Panel on rehabilitation in rheumatoid arthritis, GP 12: 69 (Nov.) 1955.
- 1309. Lowman, E. W.: Psychogenic rheumatism, Arch. Phys. Med. 36: 222 (Apr.) 1955.
- 1310. Lowman, E. W., Miller, S., Lee, P. R., Stein, H., King, R., and Heald, L.: Psychosocial factors in rehabilitation of the chronic rheumatoid arthritic, Ann. Rheumat. Dis. 13: 312 (Dec.) 1954.
- 1311. Lowman, E. W.: Rehabilitation of the chronic rheumatoid arthritic: a two-year progress report, Arch. Phys. Med. 36: 431 (July) 1955.
- 1312. Lowman, E. W.: Rehabilitation of the patient with chronic rheumatoid arthritis, J. Chron. Dis. 1: 628 (June) 1955.
- 1313. Lowman, E. W., Lee, P. R., and Rusk, H. A.: Total rehabilitation of the rheumatoid arthritic cripple, J. A. M. A. 158: 1335 (Aug. 13) 1955.
- 1314. Lubschez, R.: Identification of urinary 17-ketosteroids in rheumatic fever, Pediatrics 15: 537 (May) 1955.
- 1315. Lucas, J. E.: Diagnosis and treatment of gout, Am. Pract. and Digest Treat. 6: 871 (June) 1955.
- 1316. Ludwig, A. O.: Psychiatric considerations in rheumatoid arthritis, M. Clin. North America 39: 447 (Mar.) 1955.
- 1317. Lumpkin, Wm. R., and Firor, W. M.: Evaluation of the Bryson treatment of arthritis, Am. Surgeon 20: 756 (July) 1954.
- 1318. Lundy, J. S.: Successful chemical sympathectomy for left-sided shoulder pain after a cerebrovascular accident, Journal Lancet 75: 325 (July) 1955.
- 1319. Luse, S. A., Rusted, I. E., and Edwards, J. E.: Aschoff bodies in surgically resected left auricular appendages and elsewhere in the heart in mitral stenosis, Lab. Invest. 3: 483 (Nov.-Dec.) 1954.
- 1320. Lyell, A., and Church, R.: The cutaneous manifestations of polyarteritis nodosa, Brit. J. Dermat. 66: 335 (Oct.) 1954.
- 1321. MacAusland, W. R.: Endoprostheses in joint lesions, J. Internat. Coll. Surgeons 21: 282 (Mar.) 1954.
- 1322. MacCarthy, J. M., and Jackson, R. T.: Hepatic necrosis and other visceral lesions associated with phenylbutazone therapy, Brit. M. J. 2: 240 (July 23) 1955.
- 1323. MacDonald, H. N. A., Dodge, H. W., Jr., and Clark, E. C.: Anterior cervical-cord compression simulating degenerative disease, Proc. Staff Meet., Mayo Clin. 30: 154 (Apr. 20) 1955.
- 1324. MacFarlane, D. A.: Intestinal sarcoidosis, Brit. J. Surg. 42: 639 (May) 1955.
- 1325. MacKenzie, D. A., and Janes, J. M.: Postmenopausal osteoporosis: a programme of treatment in 42 cases, Canad. M. A. J. 71: 339 (Oct.) 1954.
- 1326. MacKenzie, I. G.: Chemotherapy in skeletal tuberculosis, Lancet 1: 652 (Mar. 27) 1954.
- 1327. MacKnight, J. C., Irby, R., and Toone, E. C., Jr.: Phenylbutazone in management of rheumatoid arthritis, rheumatoid spondylitis, and gouty arthritis, Geriatrics 9: 111 (Mar.) 1954.
- 1328. MacLean, K., and Robinson, H. S.: Sjogren's syndrome, Canad. M. A. J. 71: 597 (Dec.) 1954.
- 1329. MacLennan, J. D.: Bacterial collagenases, Bull. New York Acad. Med. 30: 997 (Dec.) 1954.
- 1330. MacMahon, H. E., Robbins, S. L., and Patterson, J. F.: Gouty nephritis, Bull. New England M. Center 16: 90 (June) 1954.

- 1331. MacNab, I.: Low back pain, the hyperextension syndrome, Canad. M. A. J. 73: 448 (Sept. 15) 1955.
- 1332. Mahaffey, H. W.: Simplified technique of injection of hydrocortisone in knee joint, J. A. M. A. 156: 312 (Sept. 25) 1954.
- 1333. Maher, J. A.: Dural nodules in rheumatoid arthritis, Arch. Path. 58: 354 (Oct.) 1954.
- 1334. Mahler, H. R., Hübscher, G., and Baum, H.: Studies on uricase. I. Preparation, purification, and properties of a cuproprotein, J. Biol. Chem. 216: 625 (Oct.) 1955.
- 1335. Mahoney, J. P., Sandberg, A. A., Gubler, C. J., Cartwright, G. E., and Wintrobe, M. M.: Uric acid metabolism in hepatolenticular degeneration, Proc. Soc. Exper. Biol. and Med. 88: 427 (Mar.) 1955.
- 1336. Mahrer, P. R., Evans, J. A., and Steinberg, I.: Scleroderma: relation of pulmonary changes to esophageal disease, Ann. Int. Med. 40: 92 (Jan.) 1954.
- 1337. Malamud, N., and Saver, G.: Neuropathologic findings in disseminated lupus erythematosus, Arch. Neurol. and Psychiat. 71: 723 (June) 1954.
- 1338. Malhotra, R. P.: Rheumatic heart disease complicated with rheumatoid arthritis, J. Indian M. A. 24: 416 (Mar.) 1955.
- 1339. Malkinson, F. D., and Wells, G. C.: Adrenal steroids in periarteritis nodosa, Arch. Dermat. and Syph. 71: 492 (Apr.) 1955.
- 1340. Mallett, B. L., and Zilkha, K. J.: Compression of the ulnar nerve at the wrist by a ganglion, Lancet 1: 890 (Apr. 30) 1955.
- 1341. Malm, P.: Indications for operative treatment of tendinitis calcarea, Acta chir. Scandinav. 109: 442, 1955.
- 1342. Manchester, B., Scotti, T. M., Reynolds, M. L., and Dawson, W. H.: Aschoff bodies in left auricular appendages of patients with mitral stenosis, clinico-pathologic study, including postoperative follow-up, Arch. Int. Med. 95: 231 (Feb.) 1955.
- 1343. Manner, H. W.: The effect of cortisone acetate on the wound healing phase of trituturs viridescens, Growth 19: 169 (Sept.) 1955.
- 1344. Manning, R. A., and Pierik, M. G.: Medical treatment of degenerative arthritis of the hip joint, Rhode Island M. J. 37: 609 (Nov.) 1954.
- 1345. Mansuy, L.: Results of surgical treatment of refractory sciatica, Arch. Surg. 70: 609 (Apr.) 1955.
- 1346. Manter, W. B.: Late reaction to hydralazine (Apresoline) therapy, New England J. Med. 250: 835 (May 13) 1954.
- 1347. See 1373 (a).
- 1348. Mantle, J. A.: Brucellar spondylitis, J. Bone and Joint Surg. 37B: 456 (Aug.) 1955.
- 1349. Margolis, H. M., Barr, J. H., Jr., Stolzer, B. L., Eisenbeis, C. H., Jr., and Martz, E. W., Jr.: Effects of prednisone (Meticorten) on manifestations of rheumatoid arthritis, J. A. M. A. 158: 454 (June 11) 1955.
- 1350. Margulies, M. E., Katz, I., and Rosenberg, M.: Spontaneous dislocation of the atlanto-axial joint in rheumatoid spondylitis, recovery from quadriplegia following surgical decompression, Neurology 5: 290 (Apr.) 1955.
- 1351. Markowitz, M., and Hemphill, W.: A comparison of oral N,N'-dibenzylethylenediamine dipenicillin G and sulfonamides for the prevention of streptococcal infections and recurrences of rheumatic fever, Antibiotics Ann. 2: 83, 1954-55.
- 1352. Markowitz, M., and Kuttner, A. G.: The effect of intensive and prolonged therapy with cortisone and hydrocortisone in first attacks of rheumatic carditis, Pediatrics 16: 325 (Sept.) 1955.
- 1353. Marks, K. L.: Congenital syphilis diagnosed by bone changes, Brit. M. J. 1: 1018 (May 1) 1954.
- 1354. Marmont, A.: Value and limitations of the L. E. cell test in the syndrome known as systemic lupus erythematosus without skin eruptions, Acta hæmat. 13: 257 (May) 1955.

- 1355. Marson, F. G. W.: Complete relief from gout, Lancet 2: 360 (Aug. 20) 1955.
- 1356. Marson, F. G. W.: Sodium salicylate and probenecid in the treatment of chronic gout, assessment of their relative effects in lowering serum uric acid levels, Ann. Rheumat. Dis. 13: 233 (Sept.) 1954.
- 1357. Martens, V. E.: Unusual synovial tumors, J. A. M. A. 157: 888 (Mar. 12) 1955.
- 1358. Martin, G. M., and Corbin, K. B.: An evaluation of conservative treatment for patients with cervical disk syndrome, Arch. Phys. Med. 35: 87 (Feb.) 1954.
- 1359. Martin, G. M., and Corbin, K. B.: An evaluation of conservative treatment for patients with cervical disk syndrome, Proc. Staff Meet., Mayo Clin. 29: 324 (June 2) 1954.
- 1360. Martin, M. M.: Neuropathic lesions of the feet in diabetes mellitus, Proc. Roy. Soc. Med. 47: 139 (Feb.) 1954.
- 1361. Martin, P.: Raynaud's phenomenon, J. Irish M. A. 36: 53 (Feb.) 1955.
- 1362. Martin, W. J., Underdahl, L. O., Mathieson, D. R., and Pugh, D. G.: Alkaptonuria: report of 12 cases, Ann. Int. Med. 42: 1052 (May) 1955.
- 1363. Martz, C. D.: Lumbar nuclear herniation and resulting physical impairment, J. Indiana M. A. 48: 33 (Jan.) 1955.
- 1364. Marx, F. J., and Berenbaum, A. A.: Systemic blastomycosis, cause of an obscure infection in a nonendemic area, New England J. Med. 251: 56 (July 8) 1954.
- 1365. Mason, G. D., Selle, W. A., and McKee, J. W.: Some physiological aspects of joints in health and disease. Part II. Physiology of abnormal joints, Am. J. Phys. Med. 33: 239 (Aug.) 1954.
- 1366. Mason, R. M.: Effect of phenylbutazone on uric acid metabolism, Brit. M. J. 1: 788 (Apr. 3) 1954.
- 1367. Mason, R. M.: Gout, Post-Grad. M. J. 31: 623 (Dec.) 1955.
- 1368. Mason, R. M.: Studies on the effect of probenecid ("Benemid") in gout, Ann. Rheumat. Dis. 13: 120 (June) 1954.
- 1369. Massell, B. F.: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis, New England J. Med. 251: 183, 221, 263 (July 29, Aug. 5, 12) 1954.
- 1370. Massell, B. F.: Hormone treatment of rheumatic carditis, Bull. Rheumat. Dis. 6: 99 (Dec.) 1955.
- 1371. Masturzo, A.: Vertebral traction for treatment of sciatica, Rheumatism 11: 62 (July) 1955.
- 1372. Mather, G., Dawson, J., and Hoyle, C.: Liver biopsy in sarcoidosis, Quart. J. Med. 24: 331 (Oct.) 1955.
- 1373. (a) Mather, H. G.: Unusual rheumatoid arthritis (arthritis mutilans), Proc. Roy. Soc. Med. 47: 457 (June) 1954.
 - (b) Mathews, M. B., Kulonen, E., and Dorfman, A.: Studies in procollagen. II. Viscosity and molecular weight, Arch. Biochem. 52: 247 (Sept.) 1954.
- 1374. Mathias, D. W.: Scleromalacia perforans, associated with retinitis pigmentosa and rheumatoid arthritis: report of a case, Am. J. Ophth. 39: 161 (Feb.) 1955.
- 1375. Mathur, T. N.: Rheumatoid arthritis treated with A. C. T. H., J. Indian M. A. 23: 508 (Aug.) 1954.
- 1376. Matthews, H. L., and Meynell, M. J.: Acute diffuse lupus erythematosus, report of a case with predominant pulmonary manifestations, Brit. M. J. 2: 1140 (Nov. 13) 1954.
- 1377. Mattingly, S.: Hypertrophic osteoarthropathy presenting as polyarthritis, Ann. Phys. Med. 2: 57 (Apr.) 1954.
- 1378. Mattox, V. R., Mason, H. L., and Albert, A.: Isolation of a sodium-retaining substance from beef adrenal extract, Proc. Staff Meet, Mayo Clin. 28: 569 (Oct. 7) 1053
- 1379. Mattsson, R.: Recurrent retinitis in Reiter's disease, Acta ophth. 33: 403, 1955.
- 1380. Maudsley, R. H.: Dysplasia epiphysalis multiplex, a report of fourteen cases in three families, J. Bone and Joint Surg. 37B: 228 (May) 1955.

- 1381. Mauer, E. F.: The toxic effects of phenylbutazone (Butazolidin), review of the literature and report of the twenty-third death following its use, New England J. Med. 253: 404 (Sept. 8) 1955.
- 1382. May, F.: A study in focal infection and its relation to rheumatic disease, Arch. Phys. Med. 36: 751 (Dec.) 1955.
- 1383. Mayer, J. A., and Barry, D. M.: Spontaneous compression of the median nerve in the carpal tunnel, New England J. Med. 251: 255 (Aug. 12) 1954.
- 1384. Mayer, J. H.: Arthroplasty of knee, Proc. Roy. Soc. Med. 48: 618 (Aug.) 1955.
- 1385. Mazet, R., Jr.: Skeletal lesions of coccidioidomycosis, Arch. Surg. 70: 497 (Apr.) 1955.
- 1386. McBride, E. D.: Disability evaluation, J. Internat. Coll. Surgeons 24: 341 (Sept.) 1955.
- 1387. McCabe, E. S., and Fittipoldi, J.: Atypical disseminated lupus erythematosus, Am. Pract. and Digest Treat. 5: 292 (Apr.) 1954.
- 1388. McCallum, A. G.: Sinusitis, granuloma of the nose and periarteritis nodosa, J. Laryng. and Otol. 68: 560 (Aug.) 1954.
- 1389. McCarty, M.: Nature of rheumatic fever, Circulation 14: 1138 (Dec.) 1956.
- 1390. McCarty, M., and Lancefield, R. C.: Variation in the group-specific carbohydrate of group A streptococci. I. Immunochemical studies on the carbohydrates of variant strains, J. Exper. Med. 102: 11 (July) 1955.
- 1391. McClary, A. R., Meyer, E., and Weitzman, E. L.: Observations on the role of the mechanism of depression in some patients with disseminated lupus erythematosus, Psychosom. Med. 17: 311 (July/Aug.) 1955.
- 1392. McClendon, R. L.: Gout, J. Kentucky M. A. 53: 120 (Feb.) 1955.
- 1393. McClure, C., Holland, H. C., and Woodhall, B.: A method for the quantitative determination of hyaluronic acid in the human intervertebral disk, Science 119: 189 (Feb. 5) 1954.
- 1394. McCormick, W. J.: Intervertebral-disc lesions: a new etiological concept, Arch. Pediat. 71: 29 (Jan.) 1954.
- 1395. McCormick, W. J.: The rheumatic diseases, is there a common etiologic factor?, Arch. Pediat. 72: 107 (Apr.) 1955.
- 1396. McCoy, F. W., Patterson, M., and Freyberg, R. H.: A study of disseminated lupus erythematosus diagnosed in patients formerly considered to have rheumatoid arthritis, Ann. Rheumat. Dis. 14: 415 (Dec.) 1955.
- 1397. McCracken, W. J.: The role of trauma in arthritis, Ontario Workmen's Compensation Board, Indust. Med. 24: 327 (July) 1955.
- 1398. McCrea, L.: Formation of uric acid calculi during chemotherapy for leukemia, J. Urol. 73: 29 (Jan.) 1955.
- 1399. McCue, C. M., Gibson, C. D., Jr., and Lindemann, L. C.: A comparison of intramuscular benzathine penicillin and oral sulfonamide in the control of rheumatic recurrences, J. Pediat. 47: 450 (Oct.) 1955.
- 1400. McCue, C. M.: A follow-up study of suspected rheumatic fever patients, J. Pediat. 44: 290 (Mar.) 1954.
- 1401. McDermott, I. K., and Wensley, E.: We can help arthritic patients, Nursing Outlook 3: 582 (Nov.) 1955.
- 1402. McEvedy, B. V.: Cystic ganglia, their pathology, natural history and treatment, Medicine Illus. (London) 9: 425 (July) 1955.
- 1403. McEwen, C., and Ziff, M.: Basic sciences in relation to rheumatic diseases, M. Clin. North America 39: 765 (May) 1955.
- 1404. McEwen, C.: Recent advances in diagnosis and treatment of rheumatic fever, M. Clin. North America 39: 353 (Mar.) 1955.
- 1405. McEwen, C., Wilson, H., and Ziff, M.: Studies on the metabolism of adrenal cortical steroids in the synovial cavity in rheumatoid arthritis, Tr. A. Am. Physicians 67: 97, 1954.

- 1406. McEwen, C.: The treatment of rheumatic fever, Am. J. Med. 17: 794 (Dec.) 1954.
- 1407. McFarland, B.: My present attitude to osteo-arthritis of the hip, J. Bone and Joint Surg. 36A: 476 (June) 1954.
- 1408. McHolick, W. J., and Scott, R. M.: Atypical chondro-osteodystrophy, Guthrie Clin. Bull. 24: 179 (Apr.) 1955.
- 1409. McIntire, R. T.: America needs the older handicapped worker, J. Am. Geriatrics Soc. 2: 203 (Apr.) 1954.
- 1410. McKeever, D. C.: Patellar prosthesis, J. Bone and Joint Surg. 37A: 1074 (Oct.) 1955.
- 1411. McKusick, V. A.: Heritable disorders of connective tissue. I. The clinical behavior of hereditary syndromes, J. Chron. Dis. 2: 491 (Nov.) 1955.
- 1412. McKusick, V. A.: Heritable disorders of connective tissue. II. The biology of normal connective tissue, J. Chron. Dis. 2: 500 (Nov.) 1955.
- 1413. McLaughlin, H. L.: "Calcified deposits" in the subdeltoid bursa, Bull. Rheumat. Dis. 4: 48 (Feb.) 1954.
- 1414. McLaurin, H. J.: Foundation president's report, J. Michigan M. Soc. 54: 268 (Mar.) 1955
- 1415. McLean, F. C.: The physiologic turnover of the mineral of bone, in Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 133.
- 1416. McLean, L. D.: Calcinosis, South. M. J. 48: 354 (Apr.) 1955.
- 1417. McMorrow, K. J.: Diagnosis and treatment of cervical spondylosis, GP 9: 64 (June)
- 1418. McSwiney, R. R., Clayton, B. E., and Prunty, F. T. G.: Ascorbic-acid metabolism after administration of corticotrophin, Lancet 1: 178 (Jan. 23) 1954.
- 1419. Meacham, G. C., and Weisberger, A. S.: Unusual manifestations of disseminated lupus erythematosus, Ann. Int. Med. 43: 143 (July) 1955.
- 1420. Medical Research Council: A comparison of cortisone and aspirin in the treatment of early cases of rheumatoid arthritis, Brit. M. J. 1: 1223 (May 29) 1954.
- 1421. Medical Research Council and American Council on Rheumatic Fever: The treatment of acute rheumatic fever in children, a cooperative clinical trial of ACTH, cortisone and aspirin, Circulation 11: 343 (Mar.) 1955.
- 1422. Medical Research Council and Nuffield Foundation: A comparison of cortisone and codeine medication as an adjuvant to manipulation in rheumatoid arthritis, Brit. M. J. 1: 233 (Jan. 30) 1954.
- 1423. Meleney, F. L., and Johnson, B. A.: A review of systemic bacitracin therapy, U. S. Armed Forces M. J. 6: 834 (June) 1955.
- 1424. Mendeloff, J.: Myocardial changes in dermatomyositis, North Carolina M. J. 15: 15 (Jan.) 1954.
- 1425. Mendelsohn, H. A., and Alban, S. L.: Complications in replacement arthroplasty of the hip, J. Bone and Joint Surg. 36A: 30 (Jan.) 1954.
- 1426. Mendelsohn, H., and Becker, B. N.: Complications in replacement arthroplasty of the hip, experience with 68 additional cases, Clin. Orthop. 6: 48, 1955.
- 1427. Menkin, V.: On the anti-inflammatory mechanism of hydrocortisone (compound F), Science 120: 1026 (Dec. 17) 1954.
- 1428. Mensor, M. C.: Non-operative treatment, including manipulation, for lumbar intervertebral disc syndrome, J. Bone and Joint Surg. 37A: 925 (Oct.) 1955.
- 1429. Mercer, W.: The management of the tuberculous hip joint, J. Bone and Joint Surg. 36A: 1123 (Dec.) 1954.
- 1430. Mercer, W.: The surgery of rheumatoid arthritis, Bull. Hosp. Joint Dis. 15: 101 (Oct.) 1954.
- 1431. Merrell, M., and Shulman, L. E.: Determination of prognosis in chronic disease. illustrated by systemic lupus erythematosus, J. Chron. Dis. 1: 12 (Jan.) 1955.

- 1432. Merrill, A. P.: Help care for the aged sick, Hosp. Management 79: 45 (May) 1955.
- 1433. Merrill, J. A.: Cortisone in disseminated lupus erythematosus during pregnancy, report of a case and review of the literature, Obst. and Gynec. 6: 637 (Dec.) 1955.
- 1434. Mestler, G. E.: A galaxy of old Japanese medical books with miscellaneous notes on early medicine in Japan. II. Acupuncture and moxibustion. Bathing, balneotherapy and massage. Nursing, pediatrics, and hygiene. Obstetrics and gynecology, Bull. M. Library A. 42: 468 (Oct.) 1954.
- 1435. Mettier, S. R.: Rheumatoid arthritis, diagnosis in peripheral joint affliction, California Med. 82: 181 (Mar.) 1955.
- 1436. Mettier, S. R.: Treatment of rheumatoid arthritis, GP 10: 89 (July) 1954.
- 1437. Meyer, K., Davidson, E. A., Linker, A., and Hoffman, P.: Studies on ground substances of connective tissue, Science 120: 785 (Nov. 12) 1954.
- 1438. Meyers, R. I.: Rehabilitation and rheumatism, M. J. Australia 2: 668 (Oct. 22) 1955.
- 1439. Meyler, L.: Drug allergy, Acta Allergol. 9: 137, 1955.
- 1440. Meyler, L.: Phagocytosis in drug allergy, Acta med. Scandinav. 150: 33, 1954.
- 1441. Miall, W. E.: Rheumatoid arthritis in males, an epidemiological study of a Welsh mining community, Ann. Rheumat. Dis. 14: 150 (June) 1955.
- 1442. Michele, A. A.: Scapulocostal syndrome, its mechanism and diagnosis, New York State J. Med. 55: 2485 (Sept. 1) 1955.
- 1443. Michelson, H. E.: Review and appraisal of present knowledge concerning lupus erythematosus, Arch. Dermat. and Syph. 69: 694 (June) 1954.
- 1444. Middleton, W. S.: Collagen disturbances encountered in general practice, Postgrad. Med. 17: 107 (Feb.) 1955.
- 1445. Middleton, W. S.: The riddle of sarcoidosis (Hutchinson-Boeck) granulomatosis, Ann. Int. Med. 41: 465 (Sept.) 1954.
- 1446. Mikhail, I. K.: Selective contracture of the flexor digitorum sublimis muscle to the ring finger, J. Bone and Joint Surg. 37B: 612 (Nov.) 1955.
- 1447. Miki, I., and Morisaki, N.: Pathological physiology in low-back pain, J. Bone and Joint Surg. 36A: 195 (Jan.) 1954.
- 1448. Mikkelsen, W. M., Salin, R. S., and Duff, I. F.: Alopecia totalis after desacetyl-methylcolchicine therapy of acute gout; report of a case, New England J. Med. 255: 769 (Oct. 18) 1956.
- 1449. Milch, H.: Brachial palsy after manipulation of frozen shoulder, New England J. Med. 250: 429 (Mar. 11) 1954.
- 1450. Milch, H.: Whip-lash injury of the lumbar neural arch, Bull. Hosp. Joint Dis. 15: 163 (Oct.) 1954.
- 1451. Miles, J., and Elrick, H.: Pseudo-pseudohypoparathyroidism, report of new case, J. Clin. Endocrinol. 15: 576 (May) 1955.
- 1452. Miller, D. S., and Lichtman, W. F.: Diabetic neuropathic arthropathy of feet, Arch. Surg. 70: 513 (Apr.) 1955.
- 1453. Miller, G., Hoyt, J. C., and Pollock, B. E.: Bilateral renal vein thrombosis and the nephrotic syndrome, associated with lesions of polyarteritis nodosa, Am. J. Med. 17: 856 (Dec.) 1954.
- 1454. Miller, H.: Polyarteritis nodosa, Practitioner 173: 133 (Aug.) 1954.
- 1455. Miller, P. B., and Sandweiss, D. J.: Perforation of a post-gastrectomy stomal ulcer during cortisone therapy, Harper Hosp. Bull. 12: 199 (Nov.-Dec.) 1954.
- 1456. Miller, P. B.: Treatment of rheumatoid arthritis with prednisone (Meticorten)—a preliminary report, Harper Hosp. Bull. 13: 135 (July-Aug.) 1955.
- 1457. Miller, R. D., Getry, R. W., Zinsser, H. H., and Schlueter, F. E.: Total adrenalectomy in rheumatoid arthritis, Lancet 2: 598 (Sept. 18) 1954.
- 1458. Millikan, C. H.: The problem of evaluating treatment of protruded lumbar intervertebral disk, observations of results of conservative and surgical treatment in 429 cases, J. A. M. A. 155: 1141 (July 24) 1954.

- 1459. Milner, P. F.: Nasal granuloma and periarteritis nodosa, Brit. M. J. 2: 1597 (Dec. 31) 1955.
- 1460. Minaisy, A.: Osteo-chondromatosis of the knee joint, J. Egyptian M. A. 37: 660, 1954.
- 1461. Mintz, B., and Goldwater, L. J.: Occupational aspects of rheumatic diseases, a review, Indust. Med. 23: 335 (Aug.) 1954.
- 1462. Mitchell, D., and MacCarthy, J.: Dermatomyositis, Irish J. M. Sc. 6: 468 (Oct.) 1955.
- 1463. Mitchell, J.: Diagnosis of rheumatic fever, J. Louisiana M. Soc. 107: 68 (Feb.) 1955.
- 1464. Mizumachi, S., and Toriyama, N.: A treatment of baseball shoulder, Yokohama M. Bull. 6: 93 (Apr.) 1955.
- 1465. Moberg, E.: The shoulder-hand-finger syndrome as a whole, Acta chir. Scandinav. 109: 284, 1955.
- 1466. Moffett, B. C., Jr.: Studies on synovial permeability. I. Direct measurements of synovial permeability in rats, Anat. Rec. 118: 813 (Apr.) 1954.
- 1467. Moffett, B. C., Jr.: Studies on synovial permeability. II. Factors influencing synovial permeability in the rat, Anat. Rec. 118: 825 (Apr.) 1954.
- 1468. Mohler, D. N., Wallin, D. G., and Dreyfus, E. G.: Studies in the home treatment of streptococcal disease. I. Failure of patients to take penicillin by mouth as prescribed, New England J. Med. 252: 1116 (June 30) 1955.
- 1469. Moldawer, M.: Senile osteoporosis, the physiological basis of treatment, Arch. Int. Med. 96: 202 (Aug.) 1955.
- 1470. Montgomery, P. O'B.: A characterization of basophilic degeneration of collagen by histochemical and microspectroscopic procedures, J. Invest. Dermat. 24: 107 (Feb.) 1955.
- 1471. Montgomery, W. W., Perone, P. M., and Schall, L. A.: Arthritis of the cricoarytenoid joint, Ann. Otol., Rhin. and Laryng. 64: 1025 (Dec.) 1955.
- 1472. Moor, F. B.: Simple physical therapy in rheumatic disease, Postgrad. Med. 16: 144 (Aug.) 1954.
- 1473. Moore, J. E.: The natural history of chronic illness, J. Chron. Dis. 1: 335 (Mar.) 1955.
- 1474. Moore, J. E., and Lutz, W. B.: The natural history of systemic lupus erythematosus: an approach to its study through chronic biologic false positive reactors, J. Chron. Dis. 1: 297 (Mar.) 1955.
- 1475. Mora, F. B., and LLamedo, L. P.: Experimental studies on the treatment of bone and joint tuberculosis with dihydrostreptomycin and isonicotinic acid hydrazide, J. Bone and Joint Surg. 37A: 156 (Jan.) 1955.
- 1476. Morgan, A. A.: Agranulocytosis caused by cinchophen, Brit. M. J. 2: 28 (July 3) 1954.
- 1477. Morgan, W. S.: The probable systemic nature of Mikulicz's disease and its relation to Sjogren's syndrome, New England J. Med. 251: 5 (July 1) 1954.
- 1478. Morgans, M. E., and Trotter, W. R.: The anti-thyroid effect of phenylbutazone. Lancet 2: 164 (July 23) 1955.
- 1479. Morris, C. J. O. R.: Biochemistry of A. C. T. H. and adrenocortical hormones. Internat. Arch. Allergy 6: 316, 1955.
- 1480. Morris, H. D.: Treatment of osteoarthritis of the hip joint, J. Louisiana M. Soc. 107: 193 (May) 1955.
- 1481. Morris, R.: Community resources for the chronically ill, J. Chron. Dis. 2: 267 (Sept.) 1955.
- 1482. Morrison, L. F.: The cervical spine and the globus syndrome, Ann. Otol., Rhin. and Laryng. 64: 753 (Sept.) 1955.
- 1483. Morrison, L. F.: Pathology of the cervical spine as a cause of pain and discomfort, M. Arts and Sc. 9: 18, 1955.
- 1484. Morrison, M., and Morrison, A. N.: A micromethod for demonstration of LE cells in marrow, Am. J. Clin. Path. 24: 1120 (Sept.) 1954.

- 1485. Morrison, R. J. G.: Discussion on some aspects of ankylosing spondylitis, complications, Proc. Roy. Soc. Med. 48: 204 (Mar.) 1955.
- 1486. Morse, S. I., Darnell, J. E., Jr., Thomas, W. A., and Glaser, R. J.: Cardiac lesions in rabbits after pharyngeal infections with group A streptococci, Proc. Soc. Exper. Biol. and Med. 89: 613 (Aug.-Sept.) 1955.
- 1487. Mortimer, E. A., Jr., and Rammelkamp, C. H., Jr.: Prophylaxis of rheumatic fever, Circulation 14: 1144 (Dec.) 1956.
- 1488. Moss, D. G.: The estimation of Butazolidin in blood, J. Clin. Path. 7: 344 (Nov.) 1954.
- 1489. Moss, J. A.: The carbohydrate of collagen, Biochem. J. 61: 151 (Sept.) 1955.
- 1490. Movat, H. Z., and More, R. H.: Morphologic evidence for the hypersensitive pathogenesis of collagen disease and its experimental counterpart, First Canadian Conference on Rheumatic Diseases, Toronto, March, 1955, p. 65.
- 1491. Mowrey, F. H., and Lundberg, E. A.: The clinical manifestations of essential polyangiitis (periarteritis nodosa), with emphasis on the hepatic manifestations. Ann. Int. Med. 40: 1145 (June) 1954.
- 1492. Muehrcke, R. C., Kark, R. M., Pirani, C. L., Pollak, V. E., and Steek, I. E.: Histological and clinical evolution of lupus nephritis, Ann. Rheumat. Dis. 14: 371 (Dec.) 1055.
- 1493. Mueller, E. E., Mead, S., Schulz, B. F., and Vaden, M. R.: A placebo-controlled study of ultrasound treatment for periarthritis, Am. J. Phys. Med. 33: 31 (Feb.) 1954.
- 1494. Mugler, A.: Effect of colchicine on eosinophil in the hypophysectomized rat, Proc. Soc. Exper. Biol. and Med. 86: 471 (July) 1954.
- 1495. Muir, A., and Cossar, I. A.: Aspirin and ulcer, Brit. M. J. 2: 7 (July 2) 1955.
- 1496. Muldoon, J. P., Berg, A. M., and Kinnaird, D. W.: Surgical implications of non-thrombocytopenic purpura, Ann. Surg. 142: 817 (Nov.) 1955.
- 1497. Mulholland, H. F., and O'Connell, J. H.: Stigmonene bromide in the treatment of muscular spasm, Journal Lancet 74: 90 (Mar.) 1954.
- 1498. Muller, J. C., Rast, C. L., Jr., Pryor, W. W., and Orgain, E. S.: Late systemic complications of hydralazine (Apresoline) therapy, J. A. M. A. 157: 894 (Mar. 12)
- 1499. Muller, R.: The arthritic foot: a method of taking weight-bearing impressions for the making of supports, Arch. Phys. Med. 36: 244 (Apr.) 1955.
- 1500. Mullins, J. F., Kirk, J. M., and Shapiro, E. M.: Chloroquine treatment of lupus erythematosus, South. M. J. 48: 732 (July) 1955.
- 1501. Murley, A. H. G.: Tennis-elbow treated with hydrocortisone acetate, Lancet 2: 223 (July 31) 1954.
- 1502. Murnaghan, G. F., and McIntosh, D.: Hydrocortisone in painful shoulder, Lancet 2: 798 (Oct. 15) 1955.
- 1503. Murphy, J. P.: Protrusion or rupture of the lumbar intervertebral disks, the principal cause of low back pain with sciatica, M. Ann. District of Columbia 24: 277 (June) 1955.
- 1504. Murray, F. J., and Ludwig, K. A.: Chemotherapy of experimental L4 rat arthritis. Antibiotics and Chemotherapy 4: 684 (June) 1954.
- 1505. Murray, R. O.: Observations on cystic tuberculosis of bone, with a report of two cases, Proc. Roy. Soc. Med. 47: 133 (Feb.) 1954.
- 1506. Murtagh, F., Chamberlain, W. E., Scott, M., and Wycis, H. T.: Cervical air myelography, a review of 130 cases, Am. J. Roentgenol. 74: 1 (July) 1955.
- 1507. Mustakallio, K. K., and Sarajas, H. S. S.: Some aspects of scleroderma heart disease, Am. Heart J. 47: 437 (Mar.) 1954.
- 1508. Nabarro, J. D. N., Stewart, J. S., and Walker, G.: Clinical and metabolic effects of prednisone, Lancet 2: 993 (Nov. 12) 1955.
- 1509. Nabarro, J. D. N.: Intravenous hydrocortisone, Arch. Middlesex Hosp. 5: 79 (Apr.) 1955.

- 1510. Nachlas, I. W.: Backache-problems in diagnosis, Sinai Hosp. J., Balto. 4: 109 (June) 1955.
- 1511. Nachlas, I. W.: The Pellegrini-Stieda para-articular calcification, Clin. Orthop. 3: 121, 1954.
- 1512. Nassim, J. R., and Pilkington, T.: Multiple visceral lesions due to phenylbutazone toxicity. Brit. M. J. 2: 1028 (Oct. 30) 1954.
- 1513. Natenshon, A. L.: A new form of drug therapy in the treatment of arthritis and rheumatoid conditions, Wisconsin M. J. 53: 223 (Apr.) 1954.
- 1514. Natenshon, A. L.: Treatment of arthritis and painful spastic skeletal muscle conditions, Clin. Med. 2: 23-28 (Jan.) 1955.
- 1515. Nathan, A. S.: The use of hyaluronidase in temporomandibular disturbances, Oral Surg., Oral Med. and Oral Path. 7: 368 (Apr.) 1954.
- 1516. National Rehabilitation Association: Purposes and principles of the National Rehabilitation Association, J. Rehabil. 20: 12 (Mar.-Apr.) 1954.
- 1517. Naylor, A., Happey, F., and MacRae, T.: Changes in the human intervertebral disc with age: a biophysical study, J. Am. Geriatrics Soc. 3: 964 (Dec.) 1955.
- 1518. Naylor, A., Happey, F., and MacRae, T.: The collagenous changes in the intervertebral disk with age and their effect on its elasticity, Brit. M. J. 2: 570 (Sept. 4) 1954.
- 1519. Neu, H. N., and Reedy, W. J.: Inexpensive mechanized interrupted transaction apparatus, J. A. M. A. 155: 438 (May 29) 1954.
- 1520. Neufeld, I.: Fibropathic syndromes in geriatric patients, Geriatrics 10: 318 (July) 1955.
- 1521. Neufeld, I.: Mechanical factors in the pathogenesis, prophylaxis, and management of "fibrositis" (fibropathic syndromes), Arch. Phys. Med. 36: 759 (Dec.) 1955.
- 1522. Neurohr, F. G.: Costen's syndrome in an edentulous patient, J. Am. Dent. A. 50: 66 (Jan.) 1955.
- 1523. Neustadt, D. H., Geiger, J., and Steinbrocker, O.: Effect of post-partum plasma in rheumatoid arthritis, Ann. Rheumat. Dis. 13: 131 (June) 1954.
- 1524. Neuwirth, E.: Neurologic complications of osteoarthritis of the cervical spine, New York State J. Med. 54: 2583 (Sept. 15) 1954.
- 1525. Nevé, R. A., and Aldrich, R. A.: Porphyrin metabolism. III. Urinary and erythrocyte porphyrin in children with acute rheumatic fever, Pediatrics 15: 553 (May) 1955.
- 1526. Newman, P. H.: Modern tendencies in treatment of osteoarthritis of the hip, Arch. Middlesex Hosp. 5: 112 (Apr.) 1955.
- 1527. Newman, P. H.: Spondylolisthesis, its cause and effect, Ann. Roy. Coll. Surgeons, England 16: 305 (May) 1955.
- 1528. Nicholas, J. A., Burstein, C. L., Umberger, C. J., and Wilson, P. D.: Management of adrenocortical insufficiency during surgery, Arch. Surg. 71: 737 (Nov.) 1955.
- 1529. Nielsen, H.: Familial occurrence, gastro-intestinal symptoms and mental disturbances in hyperparathyroidism, Acta med. Scandinav. 151: 359, 1955.
- 1530. Nisbet, N. W.: Clinical and experimental study of segmental pain from the shoulder, Brit. M. J. 1: 730 (Mar. 27) 1954.
- 1531. Nisbet, N. W.: De Quervain's disease, New Zealand M. J. 53: 387 (Aug.) 1954.
- 1532. Nisbet, N. W., and Cupit, B. F.: Gargoylism: report of a case, Brit. J. Surg. 41: 404 (Jan.) 1954.
- 1533. Nobile, A., Charney, W., Perlman, P. L., Herzog, H. L., Payne, C. C., Tully, M. E., Jevnik, M. A., and Hershberg, E. B.: Microbiological transformation of steroids. I. A^{1, 4}-diene-3-ketosteroids, J. Am. Chem. Soc. 77: 4184 (Aug.) 1955.
- 1534. Norcross, B. M., Lockie, L. M., and Talbott, J. H.: Osteoarthritis, GP 11: 93 (Mar.) 1955.

- 1535. Norcross, B. M.: The treatment of arthritis, New York State J. Med. 54: 347 (Feb. 1) 1954.
- 1536. Nordin, B. E. C., and Roper, A.: Post-pregnancy osteoporosis, a syndrome?, Lancet 1: 431 (Feb. 26) 1955.
- 1537. Nordström, S.: Flicker-fusion tests in rheumatoid arthritis treated with ACTH, Acta med. Scandinav. Supp. 308: 54, 1955.
- 1538. Noring, O., and Paaby, H.: Cortisone and ACTH treatment of post-traumatic dystrophy of the extremities, Acta orthop. Scandinav. 25: 122, 1955.
- 1539. Norrlind, R.: The significance of infections in the origination of psoriasis, Acta Rheum. Scandinav. 1: 135, 1955.
- 1540. Northfield, D. W. C.: Diagnosis and treatment of myelopathy due to cervical spondylosis, Brit. M. J. 2: 1474 (Dec. 26) 1955.
- 1541. Nuzum, J. W., Jr., and Nuzum, J. W.: Polyarteritis nodosa, statistical review of one hundred seventy-five cases from the literature and report of a "typical" case, Arch. Int. Med. 94: 942 (Dec.) 1954.
- 1542. Nydick, I., Tang, J., Stollerman, G. H., Wróblewski, F., and LaDue, J. S.: The influence of rheumatic fever on serum concentrations of the enzyme, glutamic oxalacetic transaminase, Circulation 12: 795 (Nov.) 1955.
- 1543. Nyman, G. E.: EEG in rheumatic fever, Acta med. Scandinav. 149: 127, 1954.
- 1544. Oatway, W. J., Jr., and Paulsen, G. A.: Calamities from the use of cortisone in unrecognized tuberculosis, Arizona Med. 12: 275 (July) 1955.
- 1545. O'Brien, D. J., and Storey, G.: Death from hypersensitivity due to phenylbutazone, Brit. M. J. 1: 792 (Apr. 3) 1954.
- 1546. O'Brien, G. F.: Collagen diseases, M. Clin. North America 39: 125 (Jan.) 1955.
- 1547. O'Connel, J. E. A.: Involvement of the spinal cord by intervertebral disk protrusions, Brit. J. Surg. 43: 225 (Nov.) 1955.
- 1548. O'Connell, P. A., Roy, A., and Massell, B. F.: The effect of salicylate and of paraaminobenzoate on the eosinophil response to ACTH, Am. J. M. Sc. 229: 150 (Feb.) 1955.
- 1549. Odell, R. T., and Key, J. A.: Lumbar disk syndrome caused by malignant tumors of bone, J. A. M. A. 157: 213 (Jan. 15) 1955.
- 1550. Odone, D. T.: Cortisone therapy in Sydenham's chorea, Arch. Pediat. 72: 187 (June) 1955.
- 1551. Ogryzlo, M. A.: Lupus erythematosus cell reaction: its morphology and specificity, Ann. Rheumat. Dis. 14: 414 (Dec.) 1955.
- 1552. Ogston, A. G.: Examination in the ultracentrifuge, Biochem. J. 61: 696 (Dec.) 1955.
- 1553. Oka, M.: Studies on the cholinesterase activity of red cell, plasma and synovial fluid with special reference to rheumatic diseases, Acta med. Scandinav. Supp. 293, 1954.
- 1554. Oldfield, M. C.: Dupuytren's contracture, Proc. Roy. Soc. Med. 47: 361 (May) 1954.
- 1555. O'Leary, P. A.: Lupus erythematosus, GP 9: 57 (Feb.) 1954.
- 1556. O'Leary, P. A., Lambert, E. H., and Sayre, G. P.: Muscle studies in cutaneous disease, J. Invest. Dermat. 24: 301 (Mar.) 1955.
- 1557. Olhagen, B., and Liljestrand, A.: II. Persistently elevated erythrocyte sedimentation rate with good prognosis, Acta med. Scandinav. 151: 442 (June) 1955.
- 1558. Olin, T. E.: The incidence of gonorrhoeal complications, Ann. chir. et gynaec. Fenniae 43 Supp. 5: 279, 1954.
- 1559. Olson, J. A.: Oral hydrocortisone in muscle spasm, J. M. Soc. New Jersey 52: 311 (June) 1955.
- 1560. Olsson, O.: Degenerative changes of the shoulder joint and their connection with shoulder pain, a morphological and clinical investigation with special attention to the cuff and biceps tendon, Acta chir. Scandinav. 107: 258, 1954.
- 1561. Olsson, O.: Some aspects of shoulder pain, Brit. J. Phys. Med. 18: 82 (Apr.) 1955.

- 1562. Opie, L. H.: The pulmonary manifestations of generalised scleroderma (progressive systemic sclerosis), Dis. of Chest 28: 665 (Dec.) 1955.
- 1563. O'Reilly, T. J.: Treatment of rheumatoid arthritis with organic copper compounds, Brit. M. J. 1: 150 (Jan. 15) 1955.
- 1564. Orfuss, A. J.: Ehlers-Danlos syndrome, Arch. Dermat. and Syph. 71: 649 (May) 1955.
- 1565. Orr, S. F. D.: Infra-red spectroscopic studies of some polysaccharides, Biochim. et Biophys. Acta 14: 173, 1954.
- 1566. Oshrain, H. I., and Sackler, A.: Involvement of the temporomandibular joint in a case of rheumatoid arthritis, Oral Surg., Oral Med. and Oral Path. 8: 1039 (Oct.) 1955.
- 1567. Ostriker, P. J., Ostriker, M., and Lasky, M. A.: Keratitis and scleritis associated with Felty's syndrome, Arch. Ophth. 54: 858 (Dec.) 1955.
- 1568. Otten, H. A., and Boerma, F. W.: Antistreptolysin titres, L- and O- agglutinations, and agglutination of sensitized sheep cells in sera from patients with unselected internal diseases, rheumatoid arthritis, and in sera from healthy persons, Acta med. Scandinav. 149: 55, 1954.
- 1569. den Oudsten, S. A., van Leeuwen, L., and Coers, R. J.: Corticotropin-zinc: clinical observations on an ACTH preparation with prolonged action, J. Clin. Endocrinol. 14: 680 (June) 1954.
- 1570. Overbeek, G. A., Homan, J. D. H., Neutelings, J. P. J., Booy, C. J., and van der Vies, J.: Corticotropin-zinc: chemical and pharmacologic investigations on a long-acting ACTH preparation, J. Clin. Endocrinol. 14: 681 (June) 1954.
- 1571. Overton, L. M.: The local use of hydrocortisone acetate in the treatment of painful shoulders, Clin. Orthop. 4: 115, 1954.
- 1572. Pack, G. T.: End results in the treatment of sarcomata of the soft somatic tissues, J. Bone and Joint Surg. 36A: 241 (Apr.) 1954.
- 1573. Padawer, J., and Gordon, A. S.: Effects of colchicine on mast cells of the rat, Proc. Soc. Exper. Biol. and Med. 88: 522 (Apr.) 1955.
- 1574. Page, J. A.: Fatal suppression of symptoms during hormone therapy, J. Am. Geriatrics Soc. 3: 890 (Nov.) 1955.
- 1575. Page, J. A.: Two cases of fulminating pneumonia in patients on hormone therapy, Brit. M. J. 2: 1334 (Dec. 4) 1954.
- 1576. Pagel, W., and Treip, C. S.: Viscero-cutaneous collagenosis, J. Clin. Path. 8: 1 (Feb.) 1955.
- 1577. Palitz, L. L.: Review of the pathogenesis and allergic aspects of collagen diseases, Arch. Dermat. and Syph. 70: 67 (July) 1954.
- 1578. Pallis, C., Jones, A. M., and Spillane, J. D.: Cervical spondylosis, incidence and implications, Brain 77: 274, 1954.
- 1579. Palmer, T. H., Jr., Mason, P. J. H., and Adams, A. C.: Diverticulitis of the colon with perforation during cortisone and ACTH therapy, J. Maine M. A. 46: 349 (Dec.) 1955.
- 1580. Palumbo, L. T.: Low back pain and sciatica, Am. Pract. and Digest Treat. 5: Supp. 1 (Feb.) 1954.
- 1581. Parr, L. J. A.: Recent advances in arthritis, M. J. Australia 2: 358 (Sept. 3) 1955.
- 1582. Partridge, S. M., Davis, H. F., and Adair, G. S.: The chemistry of connective tissues. II. Soluble proteins derived from partial hydrolysis of elastin, Biochem. J. 61: 11 (Sept.) 1955.
- 1583. Partridge, S. M., and Davis, H. F.: The chemistry of connective tissues. III. Composition of the soluble proteins derived from elastin, Biochem. J. 61: 21 (Sept.) 1955.
- 1584. Pascale, L. R., Dubin, A., and Hoffman, W. S.: Influence of Benemid on urinary excretion of phosphate in hypoparathyroidism, Metabolism 3: 462 (Sept.) 1954.

- 1585. Pascale, L. R., Dubin, A., Bronsky, D., and Hoffman, W. S.: Inhibition of the uricosuric action of Benemid by salicylate, J. Lab. and Clin. Med. 45: 771 (May) 1955.
- 1586. Pascher, F., Sims, C. F., and Pensky, N.: Lupus erythematosus profundus (Kaposi-Irgang), J. Invest. Dermat. 25: 347 (Nov.) 1955.
- 1587. Pascher, F., Borota, A., and Davis, B.: Pitfalls in the interpretation of L. E. preparations, J. Invest. Dermat. 24: 311 (Mar.) 1955.
- 1588. Pasricha, H. R.: Tuberculosis of bone and joints, Indian J. Pediat. 21: 218 (Sept.) 1954.
- 1589. Paterson, D. E.: Radiological bone changes and angiographic findings in leprosy with special reference to the pathogenesis of "atrophic" conditions of the digits, J. Fac. Radiol., London 7: 35 (July) 1955.
- 1590. Paul, W. D., Hodges, R. E., Bean, W. B., Routh, J. I., and Daum, K.: Effects of nitrogen mustard therapy in patients with rheumatoid arthritis, Arch. Phys. Med. 35: 371 (June) 1954.
- 1591. Paull, A. M.: Occurrence of the "L. E." phenomenon in a patient with a severe penicillin reaction, New England J. Med. 252: 128 (Jan. 27) 1955.
- 1592. Paulshock, B. Z.: Surgically precipitated adrenal cortical insufficiency in a patient receiving cortisone, Delaware State M. J. 26: 15 (Jan.) 1954.
- 1593. Payne, R. W., Shetlar, M. R., Bullock, J. A., Patrick, D. R., Hellbaum, A. A., and Ishmael, W. K.: The serum polysaccharide-protein ratio (PR) as a measure of rheumatoid arthritis activity, Ann. Int. Med. 41: 775 (Oct.) 1954.
- 1594. Payne, R. W., Shetlar, M. R., Farr, C. H., Hellbaum, A. A., and Ishmael, W. K.: The value of phenylbutazone in the treatment of rheumatoid arthritis as determined by clinical response and by the serum protein-polysaccharide ratio (PR), J. Lab. and Clin. Med. 45: 331 (Mar.) 1955.
- 1595. Peabody, C. W.: Management of rheumatoid arthritis in relation to physical and surgical measures, J. Michigan M. Soc. 54: 317 (Mar.) 1955.
- 1596. Peacock, P. B.: The prevention of rheumatic fever in a Saskatchewan health region, Canad. J. Pub. Health 46: 486 (Dec.) 1955.
- 1597. Pearce, J., and Ehrlich, A.: Gastric sarcoidosis, Ann. Surg. 141: 115 (Jan.) 1955.
- 1598. Pearce, R. H., Vance, H. G., and Watson, E. M.: The chemical composition of the cutaneous connective tissue of the rat, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 1.
- 1599. Pease, G. L.: Laboratory aid in the diagnosis of lupus erythematosus, Minnesota Med. 38: 641 (Sept.) 1955.
- 1600. Pease, G. L.: Value of the "L. E." clot test as a laboratory procedure, Nebraska M. J. 40: 52 (Feb.) 1955.
- 1601. Pedersen, H. E., and Day, A. J.: Dupuytren's disease of the foot, J. A. M. A. 154: 33 (Jan. 3) 1954.
- 1602. Pelc, S. R., and Glücksmann, A.: Sulphate metabolism in the cartilage of the trachea, pinna and xiphoid process of the adult mouse as indicated by autoradiographs, Exper. Cell Res. 8: 336 (Apr.) 1955.
- 1603. Pemberton, M.: Use of phenylbutazone in rheumatoid arthritis, Brit. M. J. 1: 490 (Feb. 27) 1954.
- 1604. Pender, J. W.: Complications in anesthesia related to cortisone therapy, Wisconsin M. J. 53: 215 (Mar.) 1954.
- 1605. Pepler, W. J., and Brandt, F. A.: A contribution to the nature of the elastolytic enzyme and the structure of elastin, Brit. J. Exper. Path. 35: 41 (Feb.) 1954.
- 1606. Peräsalo, O.: Amyloid degeneration and hormonal studies on its development, Ann chir. et gynaec. Fenniae 43 Supp. 5: 308, 1954.
- 1607. Perdziak, B., and Engbring, G. M.: Sarcoidosis, J. Am. M. Women's A. 10: 69 (Mar.) 1955.

- 1608. Perkoff, G. T., Salhanick, H. A., Zarrow, M. X., Nelson, D. H., and Tyler, F. H.: Effects of administration of relaxin to human subjects, J. Clin. Endocrinol. 14: 531 (May) 1954.
- 1609. Perl, J. I.: Transabdominal anterior discographic examination, J. Internat. Coll. Surgeons 22: 76 (July) 1954.
- 1610. Perlmann, G. E., Ropes, M. W., Kaufman, D., and Bauer, W.: The electrophoretic patterns of proteins in synovial fluid and serum in rheumatoid arthritis, J. Clin. Investigation 33: 319 (Mar.) 1954.
- 1611. Perlman, P. L., and Tolksdorf, S.: Adrenocortical activity of Meticorten and Meticortelone, Federation Proc. 14: 377 (Mar.) 1955.
- 1612. Perlstein, I. B.: Histamine as a stress-combating agent in the treatment of rheumatic disease, J. Am. Geriatrics Soc. 3: 997 (Dec.) 1955.
- 1613. Permanent physical disabilities, Pamphlet No. 6, Dominion Bureau of Statistics and Department of National Health and Welfare, Ottawa, 1955.
- 1614. Perry, C. B., and Gillespie, W. A.: Intramuscular benzathine penicillin in the prophylaxis of streptococcal infection in rheumatic children, Brit. M. J. 2: 729 (Sept. 25) 1954.
- 1615. Perry, H. M., Jr., and Schroeder, H. A.: Syndrome simulating collagen disease caused by hydralazine (Apresoline), J. A. M. A. 154: 670 (Feb. 20) 1954.
- 1616. Perry, J. C.: Experimental induction of periarteritis nodosa in white rats, Proc. Soc. Exper. Biol. and Med. 89: 200 (June) 1955.
- 1617. Perttilä, M.: End-results in Legg-Calvé-Perthes disease, Ann. chir. et gynaec. Fenniae 43 Supp. 5: 290, 1954.
- 1618. Peterman, E. A.: Enzymes in the mechanism of inflammation in the rheumatic disorders, J. Michigan M. Soc. 53: 1321 (Dec.) 1954.
- 1619. Petersen, I.: An electromyographic study of the atrophied first dorsal interosseous muscle in rheumatic arthritis, Acta Rheum. Scandinav. 1: 67, 1955.
- 1620. Petersen, P. V., and Weidmann, H.: A study of the effect of various new synthetic compounds on the adrenal ascorbic acid, Acta pharmacol. et toxicol. 11: 103, 1955.
- 1621. Peterson, R. E., and Wyngaarden, J. B.: The physiological disposition and metabolic fate of hydrocortisone in man, Ann. New York Acad. Sc. 61: 297 (May 27) 1955.
- 1622. Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J.: The physiological disposition and metabolic fate of hydrocortisone in man, J. Clin. Investigation 34: 1779 (Dec.) 1955.
- 1623. Petty, H.: Orthopaedic management of rheumatoid arthritis, Physiotherapy 41: 69 (Mar.) 1955.
- 1624. Phalen, G. S.: Backache caused by vascular disease, Clin. Orthop. 5: 149, 1955.
- 1625. Phear, D. N.: Pulmonary oedema complicating the treatment of rheumatic carditis with sodium salicylate, Arch. Middlesex Hosp. 5: 172 (July) 1955.
- 1626. Phillips, D. L., and Scott, J. S.: Recurrent genital and oral ulceration with associated eye lesions, Lancet 1: 366 (Feb. 19) 1955.
- 1627. Phillips, R. W.: Reversal of renal insufficiency in gout, Arch. Int. Med. 96: 823 (Dec.) 1955.
- 1628. Pick, M. P.: Familial osteochondritis dissecans, J. Bone and Joint Surg. 37B: 142 (Feb.) 1955.
- 1629. Pike, R. M., Sulkin, S. E., and Coggeshall, H. C.: The hemagglutination test for rheumatoid arthritis, M. Clin. North America 39: 379 (Mar.) 1955.
- 1630. Pike, R. M., Sulkin, S. E., and Burdette, R. I.: Serological reactions in rheumatoid arthritis. V. The agglutination of sensitized human group O erythrocytes by rheumatoid arthritis serum, Texas Rep. Biol. and Med. 12: 138, 1954.
- 1631. Pimm, L. H.: Tuberculosis of the subdeltoid bursa, J. Bone and Joint Surg. 37B: 102 (Feb.) 1955.
- 1632. Pincus, G.: The biosynthesis of adrenal steroids, Ann. New York Acad. Sc. 61: 283 (May 27) 1955.

- 1633. Pindell, M. L.: Common lesions of the neck and shoulder and the part roentgen rays play in these conditions, Mississippi Valley M. J. 77: 217 (Nov.) 1955.
- 1634. Piney, A.: Treatment of chronic myeloid leukaemia with a colchicum derivative, Acta hæmat. 14: 83 (Aug.) 1955.
- 1635. Piper, W. N., and Helwig, E. B.: Progressive systemic sclerosis, visceral manifestations in generalized scleroderma, Arch. Dermat. and Syph. 72: 535 (Dec.) 1955.
- 1636. Pipkin, D. E., Moshein, J., and Pirkey, E. L.: The roentgen manifestations of early joint disease, Am. J. Roentgenol. 74: 1030 (Dec.) 1955.
- 1637. Pipkin, F. G.: Management of suppurative arthritis complicating artificial hips, Clin. Orthop. 6: 126, 1955.
- 1638. Pirkey, W. P.: Use of hydrocortisone in Costen's syndrome, Arch. Otolaryng. 61: 594 (May) 1955.
- 1639. Plager, J. E., Tyler, F. H., Hecht, H. H., and Samuels, L. T.: Metabolism and excretion of intravenously administered 4-C¹⁴-17-hydroxycorticosterone, J. Clin. Endocrinol, 14: 780 (July) 1954.
- 1640. Platt, D., Pigman, W., Yielding, K. L., and Holley, H. L.: Electrophoretic analysis of normal and arthritic synovial fluid, Ann. Rheumat. Dis. 14: 93 (Mar.) 1955.
- 1641. Platt, W. D., Jr., and Steinberg, I. H.: The treatment of rheumatoid arthritis with hexamethonium chloride: a preliminary report, Ann. Int. Med. 42: 816 (Apr.) 1955.
- 1642. Pobanz, D. M., Condon, J. V., and Baker, L. A.: Plasma-cell myelomatosis, report of a case with multiple large tumors involving the digits of both hands, Arch. Int. Med. 96: 828 (Dec.) 1955.
- 1643. Pojer, J., and Ninger, E.: On atypical cases of the shoulder-hand syndrome following myocardial infarction, Cardiologia 24: 215, 1954.
- 1644. Pokorny, C. A., and Hellwig, C. A.: Weber-Christian disease: a case report, J. Kansas M. Soc. 55: 70 (Feb.) 1954.
- 1645. Polachek, A. A.: Steroid diabetes, Maryland M. J. 4: 195 (Apr.) 1955.
- 1646. Pollard, M.: Two impressions of work with the Canadian Arthritis and Rheumatism Society. 1. From the London suburbs to the most westerly town in the British Commonwealth, Physiotherapy 41: 215 (July) 1955.
- 1647. Polley, H. F.: The diagnosis and treatment of rheumatoid spondylitis, M. Clin. North America 39: 509 (Mar.) 1955.
- 1648. Polley, H. F., and Slocumb, C. H.: Medical treatment of osteoarthritis, J. A. M. A. 157: 489 (Feb. 5) 1955.
- 1649. Polley, H. F., Bickel, W. H., and Dockerty, M. B.: A new punch-biopsy technic for diagnosis of joint diseases, Postgrad. Med. 18: 47 (July) 1955.
- 1650. Pond, M. H.: 17-Ketosteroid excretion in two unusual forms of rheumatoid disease, Ann. Rheumat. Dis. 13: 67 (Mar.) 1954.
- 1651. Ponseti, I. V., and Shepard, R. S.: Lesions of the skeleton and of other mesodermal tissues in rats fed sweet-pea (*Lathyrus odoratus*) seeds, J. Bone and Joint Surg. 36A: 1031 (Oct.) 1954.
- 1652. Popovici, A. F.: Polyvinyl plastic sponge in experimental orthopedic surgery: a preliminary report, Bull. Georgetown Univ. M. Center 7: 177 (May) 1954.
- 1653. Potter, R. M., and Norcross, J. R.: Spondylolisthesis without isthmus defect, Radiology 63: 678 (Nov.) 1954.
- 1654. Poulsen, H.: Inhibition of uric acid excretion in rabbits given probenecid or salicylic acid, Acta pharmacol. et toxicol. 11: 277, 1955.
- 1655. Poulsen, H., and Praetorius, E.: Tubular excretion of uric acid in rabbits, Acta pharmacol. et toxicol. 10: 371, 1954.
- 1656. Poulsen, H.: Uric acid in blood and urine of infants, Acta physiol. Scandinav. 33: 372 (Aug.) 1955.
- 1657. Power, W. H.: A case of myositis ossificans progressiva, J. Irish M. A. 34: 128 (May) 1954.

- 1658. Preston, R. L.: Musculo-skeletal function in rheumatoid arthritis, Maryland M. J. 3: 112 (Mar.) 1954.
- 1659. Preston, R. L.: The rehabilitation of the patient with rheumatoid arthritis, New York State J. Med. 55: 2887 (Oct. 15) 1955.
- 1660. Prewitt, G.: Symposium on pain in neck, shoulder and arm. III. Role of sympathetic influences, Portland Clin. Bull. 8: 111 (Mar.) 1955.
- 1661. Price, C. H. G., and Valentine, J. C.: Malignant giant-cell synovioma of phalanx, J. Clin. Path. 7: 231 (Aug.) 1954.
- 1662. Prick, J. J., Calon, P. J., and Loo, K. J. van der: The problems of chronic rheumatism in its psychological, psychiatrical and psychosomatic aspects, Fol. psychiat. et neurol. et neurochir. neerl. 57: 121, 1954.
- 1663. Pridie, K. H.: The development and nature of osteoarthritis of the hip joint, Rheumatism 11: 2 (Jan.) 1955.
- 1664. Prowse, R. B.: A fatality due to the use of gold, Brit. M. J. 2: 917 (Oct. 16) 1954.
- 1665. Prunty, F. T. G.: Steroids of adrenal cortical type including aldosterone, Practitioner 175: 89 (July) 1955.
- 1666. Prytz, B., and Zeftel, C.: Ascorbic acid and cortisone in rheumatic carditis, Bull. St. Francis Hosp. and Sanit. 11: 34 (July) 1954.
- 1667. Psaki, C. G., and Carroll, J.: Acetic acid ionization, a study to determine the absorptive effects upon calcified tendinitis of the shoulder, Physiotherapy Rev. 35: 84 (Feb.) 1955.
- 1668. Pugh, R. J., and Zinnemann, K.: Observations upon serum-penicillin levels following the intramuscular administration of penidural, Proc. Roy. Soc. Med. 48: 1103 (Nov.) 1955.
- 1669. Pugsley, W. S.: General hypertrophic osteoarthropathy, J. Oklahoma M. A. 48: 265 (Aug.) 1955.
- 1670. Purnell, D. C., Baggenstoss, A. H., and Olsen, A. M.: Pulmonary lesions in disseminated lupus erythematosus, Ann. Int. Med. 42: 619 (Mar.) 1955.
- 1671. Pyke, D. A.: Finger clubbing, validity as a physical sign, Lancet 2: 352 (Aug. 21) 1954.
- 1672. Quarten, G. C., Clark, L. D., Cobb, S., and Bauer, W.: Mental disturbances associated with ACTH and cortisone: a review of explanatory hypotheses, Medicine 34: 13 (Feb.) 1955.
- 1673. Quigley, T. B.: Checkrein shoulder: a type of "frozen" shoulder, diagnosis and treatment by manipulation and ACTH or cortisone, New England J. Med. 250: 188 (Feb. 4) 1954.
- 1674. Quin, C. E., and Binks, F. A.: Tennis elbow, Medicine Illus. (London) 9: 159 (Mar.) 1955.
- 1675. Quin, C. E., and Binks, F. A.: Tennis-elbow (epicondylalgia externa): treatment with hydrocortisone, Lancet 2: 221 (July 31) 1954.
- 1676. Quinn, R. W.: The antitoxin response of Schick-negative rheumatic and non-rheumatic subjects to diphtheria toxoid, J. Immunol. 76: 246 (Mar.) 1956.
- 1677. Raaf, J.: Surgery for cervical rib and scalenus anticus syndrome, J. A. M. A. 157: 219 (Jan. 15) 1955.
- 1678. Rabinovitch, J., and Rabinovitch, S.: Infarction of the small infestine sequent to polyarteritis nodosa of the mesenteric vessels, Am. J. Surg. 88: 896 (Dec.) 1954.
- 1679. Race, G. J., and Peschel, E.: Pathogenesis of polyarteritis nodosa in hypertensive rats, Circul. Res. 2: 483 (Nov.) 1954.
- 1680. Ragan, C.: The present-day management of arthritis, J. Chron. Dis. 1: 253 (Mar.) 1955.
- 1681. Ragan, C., Moderator: Rheumatic fever and rheumatoid arthritis, Bull. New York Acad. Med. 30: 863 (Nov.) 1954.
- 1682. Raleigh, G. W., and Kobes, H. R.: Juvenile rheumatoid arthritis. Am. Pract. and Digest Treat. 5: 954 (Dec.) 1954.

- 1683. Ralston, E. L.: Osteomyelitis of the spine due to Salmonella choleraesuis, J. Bone and Joint Surg. 37A: 580 (June) 1955.
- 1684. Ramachandran, G. N., and Ambady, G. K.: Elements of the helical structure of collagen, Current Sc. 23: 349 (Nov.) 1954.
- 1685. Ramachrandran, G. N.: Infrared spectrum and structure of collagen, J. Chem. Phys. 23: 600 (Mar.) 1955.
- 1686. Ramachandran, G. N., and Ambady, G. K.: Oriented crystallization of inorganic salts in collagen, Experientia 11: 343 (Sept.) 1955.
- 1687. Ramachandran, G. N., and Kartha, G.: Structure of collagen, Nature, London 174: 269 (Aug. 7) 1954.
- 1688. Ramachandran, G. N., and Kartha, G.: Structure of collagen, Nature, London, 176: 593 (Sept. 24) 1955.
- 1689. Ramachandran, G. N., and Kartha, G.: Studies on collagen. I. Structure of the collagen group of proteins, Proc. Indian Acad. Sc. Sect. a 42: 215, 1955.
- 1690. Ramamurthi, B.: Brachial neuritis and cervical disc prolapse, J. Indian M. A. 24: 105 (Nov.) 1954.
- 1691. Rammelkamp, C. H., Jr.: Epidemiology of streptococcal infections, Harvey Lectures 51: 113, 1955-56.
- 1692. Rammelkamp, C. H., Jr., and Stolzer, B. L.: The treatment and prevention of rheumatic fever, Pediat. Clin. North America 1: 265 (Feb.) 1954.
- 1693. Ramos, J. M.: Rheumatoid arthritis, fifteen years' experience with chrysotherapy, Rhode Island M. J. 38: 623 (Nov.) 1955.
- 1694. Ramsey, R. H., and Key, J. A.: The treatment of experimental arthritis in rabbits with hydrocortisone acetate, J. Bone and Joint Surg. 37A: 354 (Apr.) 1955.
- 1695. Randall, J. T.: Observations on the collagen system, Nature, London 174: 853 (Nov. 6) 1954.
- 1696. Rantz, L. A.: The streptococcal etiology of rheumatic fever, M. Clin. North America 39: 339 (Mar.) 1955.
- 1697. Rao, K. V. S.: An experimental study of regeneration in cartilage, J. Path. and Bact. 67: 455 (Apr.) 1954.
- 1698. Rapp, I. H.: The use of patellectomy, South. M. J. 47: 720 (Aug.) 1954.
- 1699. Rasmussen, H.: Iodide hypersensitivity in the etiology of periarteritis nodosa, J. Allergy 26: 394 (Sept.) 1955.
- 1700. Rawkins, M. D.: The diagnosis of herniation of intervertebral discs in the cervical spine, Brit. J. Phys. Med. 17: 219 (Oct.) 1954.
- 1701. Rawls, W. B.: A five-year study of adrenal steroid compounds, J. Am. Geriatrics Soc. 3: 614 (Aug.) 1955.
- 1702. Ray, R. D., Violette, D. La., Buckley, H. D., and Mosiman, R. S.: Studies of bone metabolism. I. A comparison of the metabolism of strontium⁶⁰ in living and dead bone, J. Bone and Joint Surg. 37A: 143 (Jan.) 1955.
- 1703. Reagan, R. L., Palmer, E. D., Delaha, E. C., and Brueckner, A. L.: Study by electron microscopy of erythrocytes from a patient affected with sarcoidosis, Texas Rep. Biol. and Med. 13: 350, 1955.
- 1704. Recht, L.: A case of severe gout in a woman aged 27, Acta med. Scandinav. 150: 189. 1954.
- 1705. Reddy, D. J., Rao, D. S., and Reddy, D. B.: A case of lupus erythematosus disseminatus, J. Indian M. A. 24: 391 (Feb.) 1955.
- 1706. Reddy, D. J.: Sarcoidosis—an autopsy study of two cases. J. Indian M. A. 23: 237 (Mar.) 1954.
- 1707. Redkey, H.: The community rehabilitation center, J. Rehabil. 20: 14 (May-June) 1954.
- 1708. Reece, J. M., and Reynolds, T. B.: Amyloidosis complicating rheumatoid arthritis. Am. J. M. Sc. 228: 554 (Nov.) 1954.

- 1709. Reed, C. I., and Day, W. J.: Do potentials of metabolic origin exist in the synovialis?, Am. J. Physiol. 178: 135 (July) 1954.
- 1710. Reed, C. S. H.: Acute disseminated lupus erythematosus in a child, Australasian Ann. Med. 4: 296 (Nov.) 1955.
- 1711. Reed, C. S. H.: Christmas disease, Australasian Ann. Med. 4: 219 (Aug.) 1955.
- 1712. Reed, E. B., Feightmeir, T. V., and Willett, F. M.: Zoxazolamine—a potent uricosuric agent. New England J. Med. 258: 894 (May 1) 1958.
- 1713. Refvem, O.: The pathogenesis of Boeck's disease (sarcoidosis), investigations on the significance of foreign bodies, phospholipids and hypersensitivity in the formation of sarcoid tissue, Acta med. Scandinav. Supp. 294, 1954.
- 1714. Regen, E. M.: Treatment of "the frozen shoulder," Am. Surgeon 20: 893 (Aug.)
- 1715. Reid, H. A.: Reiter's syndrome and cortisone, Ann. Rheumat. Dis. 13: 161 (June) 1954.
- 1716. Reinhardt, D. J., and Waldron, J. M.: Lupus erythematosus-like syndrome complicating hydralazine (Apresoline) therapy, J. A. M. A. 155: 1491 (Aug. 21) 1954.
- 1717. Reinhold, J.: The survival of transfused red cells in acute rheumatic fever with reference to a latent haemolytic mechanism, Arch. Dis. Childhood 29: 201 (June) 1954.
- 1718. Reiss, F., Buncke, C. M., and Caroline, L.: Coccidioidomycotic granuloma in New York City, New York State J. Med. 54: 1206 (Apr. 15) 1954.
- 1719. Rejholec, V., and Wagner, V.: Antimyocardial antibodies in rheumatic fever, Experientia 11: 278 (July) 1955.
- 1720. Renkin, E. M., and Zaun, B.: Effects of adrenal hormones on capillary permeability in perfused rat tissues, Am. J. Physiol. 180: 498 (Mar.) 1955.
- 1721. Renold, A. E., Haydar, N. A., Reddy, W. J., Goldfien, A., St. Marc, J. R., and Laidlaw, J. C.: Biological effects of fluorinated derivatives of hydrocortisone and progesterone in man, Ann. New York Acad. Sc. 61: 582 (May 27) 1955.
- 1722. Retbøll, G., Egemose, T., and Holst, J. E.: Treatment of polyarthritis chronica with nitrogen-mustard (Erasol), Acta med. Scandinav. 151: 289, 1955.
- 1723. Reynolds, E. S., Schlant, R. C., Gorick, H. C., and Damuvin, G. J.: Fatal massive necrosis of the liver as a manifestation of hypersensitivity to probenecid, New England J. Med. 256: 592 (Mar. 28) 1958.
- 1724. Reynolds, F. C., and Ramsey, R. H.: The use of hydrocortisone (compound F) in orthopedic surgery, South. M. J. 47: 209 (Mar.) 1954.
- 1725. Reynolds, W. E., and Short, C. L.: The clinical manifestations of rheumatoid arthritis, M. Clin. North America 39: 365 (Mar.) 1955.
- 1726. Reynolds, W. E., Short, C. L., and Bauer, W.: The course of rheumatoid arthritis, Bull. Rheumat. Dis. 5: 77 (Nov.) 1954.
- 1727. Rhaney, K., and Lamb, D. W.: The cysts of osteoarthritis of the hip, a radiological and pathological study, J. Bone and Joint Surg. 37B: 663 (Nov.) 1955.
- 1728. Ribbing, S.: The hereditary multiple epiphyseal disturbance and its consequences for the aetiogenesis of local malacias, particularly the osteochondrosis dissecans, Acta orthop. Scandinav. 24: 286, 1955.
- 1729. Rich, A., and Crick, F. H. C.: The structure of collagen, Nature, London 176: 915 (Nov. 12) 1955.
- 1730. Rich, R. E.: Hydrocortisone in the treatment of ganglia, J. M. Soc. New Jersey 52: 260 (May) 1955.
- 1731. Richards, H. J.: The surgical treatment of Dupuytren's contracture, J. Bone and Joint Surg. 36B: 90 (Feb.) 1954.
- 1732. Richardson, A. T.: Shoulder-hand syndrome following herpes zoster, Ann. Phys. Med. 2: 132 (Oct.) 1954.
- 1733. Riley, J. F.: Pharmacology and functions of the mast cells, Pharmacol. Rev. 7: 267 (June) 1955.

- 1734. Rindani, T. H.: Peripheral antagonism between hydrocortisone and compound S, Proc. Soc. Exper. Biol. and Med. 87: 345 (Nov.) 1954.
- 1735. Rindani, T. H.: Topical action of steroid hormones on inflammation, Arch. internat. de pharmacodyn. et de thérap. 99: 467 (Oct.) 1954.
- 1736. Rinehart, R. E.: Chloroquine therapy in rheumatoid arthritis, Northwest Med. 54: 713 (July) 1955.
- 1737. Rinehart, R. E., and Marcus, H.: Incidence of amebiasis in healthy individuals, clinic patients and those with rheumatoid arthritis, Northwest Med. 54: 708 (July) 1955.
- 1738. Rinehart, R. E.: Recent concepts of pathogenesis and treatment of gout, Northwest Med. 53: 692 (July) 1954.
- 1739. Rivelis, A., Traeger, C. H., and Rogoff, B.: Studies of relaxin therapy for progressive systemic sclerosis (generalized scleroderma) and other connective tissue diseases: a preliminary report, American Rheumatism Association Meeting, San Francisco, California, June 20, 21, 1958.
- 1740. Roantree, R. J., and Rantz, L. A.: Clinical experience with the C-reactive protein test, Arch. Int. Med. 96: 674 (Nov.) 1955.
- 1741. Robb-Smith, A. H. T.: The concept of the collagen diseases, Practitioner 173: 117 (Aug.) 1954.
- 1742. Robbins, W. C., Watson, R. F., Pappas, G. D., and Porter, K. R.: Some effects of anti-collagen serum on collagen formation in tissue culture: a preliminary report, J. Biophys. and Biochem. Cytol. 1: 381 (July 25) 1955.
- 1743. Roberts, D. W.: The over-all picture of long-term illness, J. Chron. Dis. 1: 149 (Feb.) 1955.
- 1744. Roberts, H. M., and Brunsting, L. A.: Dermatomyositis in childhood, Postgrad. Med. 16: 396 (Nov.) 1954.
- 1745. Roberts, M. H., and Sullivan, C.: Influence of the liver on bone metabolism, J. A. M. A. 159: 1002 (Nov. 5) 1955.
- 1746. Robinson, A. R., Stulberg, C. S., and Kuyper, A. C.: Identification of the substance active in sheep cell agglutination test for rheumatoid arthritis, Proc. Soc. Exper. Biol. and Med. 85: 4 (Jan.) 1954.
- 1747. Robinson, C. H.: Dietotherapy, the low purine diet, Am. J. Clin. Nutrition 2: 276 (July) 1954.
- 1748. Robinson, D., and Clary, W. U.: Osteitis condensans ilii, J. M. A. Georgia 43: 130 (Feb.) 1954.
- 1749. Robinson, E. K., and Ernst, R. W.: Boeck's sarcoid of the peritoneal cavity, Surgery 36: 986 (Nov.) 1954.
- 1750. Robinson, J. J.: Failure to produce rheumatic fever in rabbits by prolonged and intensive streptococcus infection, Arch. Path. 57: 516 (June) 1954.
- 1751. Robinson, R. A., and Watson, M. L.: Crystal-collagen relationships in bone as observed in the electron microscope. III. Crystal and collagen morphology as a function of age, Ann. New York Acad. Sc. 60: 596 (Apr. 27) 1955.
- 1752. Robinson, R. A.: The relation of the apatite inorganic crystals to the organic matrix and water of bone, in Lectures on orthopaedics and the rheumatic diseases, edited by Marguerite Clark, presented at the Scientific Conference September, 1955, Hospital for Special Surgery, New York, p. 127.
- 1753. Robinson, R. G.: Arthritis, M. J. Australia 2: 1110 (Dec. 31) 1955.
- 1754. Robinson, R. G.: Remissions induced in rheumatoid arthritis by epidemic parotitis, M. J. Australia 2: 292 (Aug. 20) 1955.
- 1755. Robinson, W. D., Duff, I. F., and Smith, E. M.: Joint fluid changes in rheumatoid arthritis, J. Michigan M. Soc. 54: 270 (Mar.) 1955.
- 1756. Robinson, W. D., and Lampe, I.: Long-range evaluation of radiotherapy in rheumatoid spondylitis, Ann. Rheumat. Dis. 7: 245 (Dec.) 1948.
- 1757. Roche, M.: A case of pseudo-pseudohypoparathyroidism, J. Clin. Endocrinol. 15: 964 (Aug.) 1955.

- 1758. Rössing, P., and Lutterbeck, H.: Hyaluronidase therapy of inflammatory and degenerative joint diseases, Rheumatism 10: 76 (Oct.) 1954.
- 1759. Rogan, M. C., Needham, C. D., and McDonald, I.: Effect of ankylosing spondylitis on ventilatory function, Clin. Sc. 14: 91 (Feb.) 1955.
- 1760. Rogers, F. B., and Lansbury, J.: Atrophy of auricular and nasal cartilages following administration of chorionic gonadotrophins in a case of arthritis mutilans with the sicca syndrome, Am. J. M. Sc. 229: 55 (Jan.) 1955.
- 1761. Rogers, F. J., and Haserick, J. R.: Sarcoidosis and the Kveim reaction, J. Invest. Dermat. 23: 389 (Nov.) 1954.
- 1762. Rogoff, B.: Rheumatoid arthritis, the need for individualized therapy, Missouri Med. 51: 1001 (Dec.) 1954.
- 1763. Romano, J.: On those who care for the sick, J. Chron. Dis. 1: 695 (June) 1955.
- 1764. Romanus, R., and Yden, S.: Destructive and ossifying spondylitic changes in rheumatoid ankylosing spondylitis (pelvo-spondylitis ossificans), Acta orthop. Scandinav. 22: 88, 1953.
- 1765. Romanus, R.: Pelvo-spondylitis ossificans in the male (ankylosing spondylitis, morbus Bechterew-Marie-Strümpell) and genito-urinary infection, Acta med. Scandinav. Supp. 280: 186, 1953.
- 1766. Ronchese, F., and Kern, A. B.: Bone lesions in Kaposi's sarcoma, Arch. Dermat. and Syph. 70: 342 (Sept.) 1954.
- 1767. Ronchese, F.: Dermatitis of the hands and analogous disorders of the nails, M. Clin. North America 39: 1317 (Sept.) 1955.
- 1768. Ronchese, F.: Pseudo-occupational marks, Indust. Med. 24: 546 (Dec.) 1955.
- 1769. Root, S. W., Andrews, G. A., Kniseley, R. M., and Tyor, M. P.: The distribution and radiation effects of intravenously administered colloidal Au¹⁰⁸ in man, Cancer 7: 856 (Sept.) 1954.
- 1770. Ropes, M. W., Perlmann, G. E., Kaufman, D., and Bauer, W.: The electrophoretic distribution of proteins in plasma in rheumatoid arthritis, J. Clin. Investigation 33: 311 (Mar.) 1954.
- 1771. Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A.: Proposed diagnostic criteria for rheumatoid arthritis, report of a study conducted by a committee of the American Rheumatism Association, J. Chron. Dis. 5: 630 (June) 1957.
- 1772. Rose, G. K.: Backache and the disc, Lancet 1: 1143 (June 5) 1954.
- 1773. Rose, G. K.: The painful heel, Brit. M. J. 2: 831 (Oct. 1) 1955.
- 1774. Rose, G. K.: Prolapsed intervertebral disc, Medicine Illus. (London) 9: 219 (Apr.) 1955.
- 1775. Rose, G. K.: Treatment of osteo-arthritis of the knee joint, Rheumatism 11: 36 (Apr.) 1955.
- 1776. Rosen, P.: Observations on the use of metacortandracin, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 57.
- 1777. Rosenberg, E. F.: Gout: a summary of recent developments in therapy, J. Am. Geriatrics Soc. 2: 229 (Apr.) 1954.
- 1778. Rosendal, K., and Faber, V.: Streptococcal hyaluronidase. III. The effect of penicillin on the production of hyaluronic acid and hyaluronidase by hemolytic streptococci (type 24, group A), Acta path. et microbiol. Scandinav. 36: 263, 1955.
- 1779. Rosendal, K., and Faber, V.: Streptococcal hyaluronidase. V. The effect of penicillin on the production of hyaluronic acid and hyaluronidase by hemolytic streptococci (type 28, group A), Acta path. et microbiol. Scandinav. 37: 293, 1955.
- 1780. Rosenfeld, A. J.: Observations on the nature and treatment of rheumatoid arthritis, J. Albert Einstein M. Center 2: 103 (May) 1954.
- 1781. Rosenfeld, S., Swiller, A. I., and Morrison, M.: Simple method of demonstrating the L. E. cell by finger puncture, J. A. M. A. 155: 568 (June 5) 1954.

- 1782. Ross, D. N.: Treatment of gout with H. P. C., Brit. M. J. 2: 782 (Oct. 2) 1954.
- 1783. Ross, D. W.: Acute suppurative arthritis of the hip in premature infants, J. A. M. A. 156: 303 (Sept. 25) 1954.
- 1784. Ross, T. L.: Rheumatic fever can be prevented, J. M. A. Georgia 44: 415 (Aug.) 1955.
- 1785. Rothbard, S., and Watson, R. F.: Amyloidosis and renal lesion induced in mice by injection with Freund-type of adjuvant, Proc. Soc. Exper. Biol. and Med. 85: 133 (Feb.) 1954.
- 1786. Rothermich, N. O.: The problem of rheumatoid arthritis from the clinician's view-point, Am. Pract. and Digest Treat. 5: 647 (Aug.) 1954.
- 1787. Round Table Conference: Management of rheumatoid arthritis, June 23, Canad. M. A. J. 73: 146 (July 15) 1955.
- 1788. Roy, L. M. H., Wigzell, F. W., Demers, R., Sinclair, R. J. G., Duthie, J. J. R., Atherden, S. M., and Marrian, G. F.: Liver function in relation to possible abnormalities of steroid metabolism in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 183 (June) 1955.
- 1789. Roy, L. M. H., Alexander, W. R. M., and Duthie, J. J. R.: Nature of anaemia in rheumatoid arthritis. I. Metabolism of iron, Ann. Rheumat. Dis. 14: 63 (Mar.) 1955.
- 1790. Rubin, E. H.: Pulmonary lesions in "rheumatoid disease" with remarks on diffuse interstitial pulmonary fibrosis, Am. J. Med. 19: 569 (Oct.) 1955.
- 1791. Ruebner, B.: The relationship between muscle damage and the Aschoff cell in rheumatic carditis, J. Path. and Bact. 68: 101 (July) 1954.
- 1792. Ruggieri, P. A.: C-reactive blood protein in inflammatory disease: its value as an index of rheumatic activity, J. M. Soc. New Jersey 52: 500 (Oct.) 1955.
- 1793. Rukes, J. M., Orr, R. H., and Forsham, P. H.: Clinical uses of intravenous hydrocortisone, Metabolism 3: 481 (Nov.) 1954.
- 1794. Rukes, J. M., Orr, R. H., Forsham, P. H., and Galante, M.: The use of intravenous hydrocortisone in major surgery, Ann. New York Acad. Sc. 61: 448 (May 27)
- 1795. Runge, C. F.: Roentgenographic examination of the lumbosacral spine in routine pre-employment examinations, J. Bone and Joint Surg. 36A: 75 (Jan.) 1954.
- 1796. Runyan, J. W., Jr., and Beebe, R. T.: Polyarteritis nodosa, GP 12: 101 (Oct.) 1955.
- 1797. Rupp, J. J., Paschkis, K. E., and Cantarow, A.: Role of potassium in the protein-catabolic effect of cortisone and ACTH, Endocrinology 56: 21 (Jan.) 1955.
- 1798. Rusk, H. A.: "A crippled child shall lead them . . . ," in Lectures on Orthopaedics and the Rheumatic Diseases, edited by Marguerite Clark, presented at the Scientific Conferences, September, 1955, Hospital for Special Surgery, New York, p. 59.
- 1799. Rusk, H. A., and Taylor, E. J.: Economic values of rehabilitation, J. Chron. Dis. 1: 222 (Feb.) 1955.
- 1800. Russek, A. S.: Role of physical medicine in relief of certain pain mechanisms of shoulder, J. A. M. A. 156: 1575 (Dec. 25) 1954.
- 1801. Sabanas, A. O., and Ghormley, R. K.: Hemangioma of the knee joint complicated by synovial chondromatosis: report of a case, Proc. Staff Meet., Mayo Clin. 30: 171 (May 4) 1955.
- 1802. Sacks, S.: The use of hydrocortisone by local and intra-articular injection in a variety of common orthopaedic conditions, South African M. J. 29: 335 (Apr. 9) 1955.
- 1803. Sagal, Z.: Periarteritis nodosa: report of a case with brain involvement, Ann. Int. Med. 42: 711 (Mar.) 1955.
- 1804. Saha, A. K.: Low backache, J. Indian M. A. 25: 171 (Aug.) 1955.
- 1805. Sainsbury, P., and Gibson, J. G.: Symptoms of anxiety and tension and the accompanying physiological changes in the muscular system, J. Neurol., Neurosurg. and Psychiat. 17: 216 (Aug.) 1954.

- 1806. Sairanen, E., Koskinen, H. M., and Holopainen, T.: On the correlation between biopsy findings and the Congo red test in rheumatoid arthritis, Acta Rheum. Scandinav. 1: 262, 1956.
- 1807. Salazar-Mallén, M., and Rulfo, J.: On some features of rheumatic fever and rheumatic heart disease as seen in the National Cardiological Institute of Mexico, Ann. Int. Med. 42: 607 (Mar.) 1955.
- 1808. Salgado, E.: Action of hypophyseal growth and thyrotrophic hormones in thyroid-ectomized rats, Ann. Rheumat. Dis. 14: 73 (Mar.) 1955.
- 1809. Salgado, E.: Influence of hypophysectomy upon the established hypertensive disease induced by desoxycorticosterone, J. Lab. and Clin. Med. 45: 865 (June) 1955.
- 1810. Salomon, A., Dougherty, E. F., Herschfus, J. A., and Segal, M. S.: Scleroderma, pulmonary and skin studies before and after treatment with cortisone, Arch. Int. Med. 95: 103 (Jan.) 1955.
- 1811. Salter, N.: Methods of measurement of muscle and joint function, J. Bone and Joint Surg. 37B: 474 (Aug.) 1955.
- 1812. Sanders, R. L.: Bone formation in upper abdominal scars, Ann. Surg. 141: 621 (May) 1955.
- 1813. Sanderud, A.: Pigmented villonodular synovitis, Acta orthop. Scandinav. 24: 155, 1954.
- 1814. Sandifer, S. H.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian syndrome): case report with response to roentgen therapy and failure of cortisone, Ann. Int. Med. 42: 451 (Feb.) 1955.
- 1815. Sands, J. H., Palmer, P. P., Mayock, R. L., and Creger, W. P.: Evidence for serologic hyper-reactivity in sarcoidosis, Am. J. Med. 19: 401 (Sept.) 1955.
- 1816. Sandweiss, D. J.: Effects of adrenocorticotropic hormone (ACTH) and of cortisone on peptic ulcer. I. Clinical review, Gastroenterology 27: 604 (Nov.) 1954.
- 1817. Sandweiss, D. J., Scheinberg, S. R., and Saltzstein, H. C.: Effects of adrenocortico-tropic hormone (ACTH) and of cortisone on peptic ulcer. II. Experimental studies on Mann-Williamson dogs, Gastroenterology 27: 617 (Nov.) 1954.
- 1818. Sanes, S., Scamurra, V., and Robins, H. M.: Laboratory aids in diagnosis of the collagen diseases, Geriatrics 10: 59 (Feb.) 1955.
- 1819. Sarnat, B. G., and Laskin, D. M.: Cartilage and cartilage implants, Internat. Abstr. Surg. 99: 521 (Dec.) 1954.
- 1820. Saslaw, M. S., Hernandez, F. A., and Werblow, S. C.: Conditions clinically confused with the rheumatic state, J. Pediat. 44: 414 (Apr.) 1954.
- 1821. Saslaw, M. S., and Streitfeld, M. M.: Group A beta hemolytic streptococci and rheumatic fever in Miami, Fla., Pub. Health Rep. 69: 877 (Sept.) 1954.
- 1822. Saslaw, M. S., and Streitfeld, M. M.: Skin response to Trafuril: possible test for rheumatic activity, J. Florida M. A. 41: 21 (July) 1954.
- 1823. Savage, O.: Cortisone and ACTH in rheumatoid arthritis, Arch. Middlesex Hosp. 5: 141 (July) 1955.
- 1824. Savastano, A. A.: Experiences with the intra-articular use of hydrocortisone acetate, Rhode Island M. J. 38: 689 (Dec.) 1955.
- 1825. Sayers, G., Glenn, E. M., Sydnor, K. L., Lipscomb, M., Sweat, M. L., Kelly, L. W., Jr., Levy, R. P., and Jefferies, W. McK.: Plasma and urinary steroids after hydrocortisone infusion, J. Clin. Investigation 34: 1600 (Nov.) 1955.
- 1826. Schajowicz, F., and Cabrini, R. L.: The effect of acids (decalcifying solutions) and enzymes on the histochemical behavior of bone and cartilage, J. Histochem. and Cytochem. 3: 122 (Mar.) 1955.
- 1827. Schalimtzek, M.: Functional roentgen examination of "degenerated" and normal intervertebral disks of the lumbar spine, Acta radiol. Supp. 116: 300, 1954.
- 1828. Scheifley, C. H.: Shoulder pain and coronary heart disease, Proc. Staff Meet., Mayo Clin. 29: 363 (June 30) 1954.

- 1829. Schepers, G. W. H.: The rheumatic lung, Indust. Med. 23: 374 (Aug.) 1954.
- 1830. Schiller, F., and Kolb, F. O.: Carpal tunnel syndrome in acromegaly, Neurology 4: 271 (Apr.) 1954.
- 1831. Schiller, S., Mathews, M. B., Jefferson, H., Ludowieg, J., and Dorfman, A.: The metabolism of mucopolysaccharides in animals. I. Isolation from skin, J. Biol. Chem. 211: 717 (Dec.) 1954.
- 1832. Schlesinger, B.: Cortisone and corticotrophin in rheumatic fever, Practitioner 175: 563 (Nov.) 1955.
- 1833. Schlesinger, B.: Errors of diagnosis in paediatrics, Brit. M. J. 1: 369 (Feb. 12) 1955.
- 1834. Schorr, S., and Adler, E.: Calcified intervertebral disc in children and adults, Acta radiol. 41: 498 (June) 1954.
- 1835. Schroeder, H. A.: Hypertensive vascular disease: therapy with modern drugs and its limits, J. Chron. Dis. 1: 497 (May) 1955.
- 1836. Schubert, R. R.: The arthritides in industry, J. M. Soc. New Jersey 51: 430 (Oct.) 1954.
- 1837. Schultz, I., Baum, J., and Ziff, M.: A new micro-method for the L. E. cell phenomenon, Proc. Soc. Exper. Biol. and Med. 88: 300 (Feb.) 1955.
- 1838. Schurr, P. H.: Sacral extradural cyst: an uncommon cause of low back pain, J. Bone and Joint Surg. 37B: 601 (Nov.) 1955.
- 1839. Schwartz, F. F.: Indications and contraindications in ultrasonic therapy, South. M. J. 47: 854 (Sept.) 1954.
- 1840. Schwartz, F. F.: Ultrasonics in the treatment of rheumatism, Rheumatism 11: 16 (Jan.) 1955.
- 1841. Schwartz, L. L.: Ethyl chloride treatment of limited mandibular movement, J. Am. Dent. A. 48: 497 (May) 1954.
- 1842. Schwartz, L. L.: Pain associated with the temporomandibular joint, J. Am. Dent. A. 51: 394 (Oct.) 1955.
- 1843. Schwartz, L. L., and Tausig, D. P.: Temporomandibular joint pain: treatment with intramuscular infiltration of tetracaine hydrochloride: a preliminary report, New York J. Dent. 20: 219 (May) 1954.
- 1844. Schwartz, N. H., Marshall, D., and Robinson, B. D.: Phenylbutazone toxicity resulting in a severe systemic reaction, New York State J. Med. 54: 265 (Jan. 15) 1954.
- 1845. Schwartz, S., Blain, H. R., Geiger, H. B., and Hartung, E. F.: Investigation of use of aurothioglycanide (Lauron) in rheumatoid arthritis, preliminary report of toxicity and therapeutic effects of a fine suspension, J. A. M. A. 154: 1263 (Apr. 10) 1954.
- 1846. Schwartz, S., Pridie, K. H., and Eyre-Brook, A. L.: A survey of acrylic arthroplasty for arthritis of the hip joint, South African M. J. 29: 625 (July 2) 1955.
- 1847. Scott, J. C.: Stress factor in the disc syndrome, J. Bone and Joint Surg. 37B: 107 (Feb.) 1955.
- 1848. Scott, R. B., and DeLilly, M. R.: Idiopathic calcinosis universalis: report of a case in a child treated with corticotropin (ACTH) and cortisone, Am. J. Dis. Child. 87: 55 (Jan.) 1954.
- 1849. Scuderi, C.: Backache, diagnosis and treatment, from an orthopedic standpoint, Post-grad. Med. 15: 301 (Apr.) 1954.
- 1850. Scuderi, C.: Diagnosis and treatment of backache—from the standpoint of the general practitioner, J. Oklahoma M. A. 47: 191 (July) 1954.
- 1851. Scuderi, C., and Khedroo, F.: Herniation of the intervertebral disc: diagnosis, treatment and resumé of follow-up study, J. Internat. Coll. Surgeons 23: 194 (Feb.) 1955.
- 1852. Scudese, V.: Primary tuberculosis of patella, Am. J. Surg. 87: 639 (Apr.) 1954.
- 1853. Seegmiller, J. E., Laster, L., and Stetten, D., Jr.: Incorporation of 4-amino-5-imidazolecarbox-amide-4-C¹⁸ into uric acid in the normal human, J. Biol. Chem. 216: 653 (Oct.) 1955.

- 1854. Seely, J. R., Ely, R. S., Done, A. K., Ainger, L. E., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. VII. Effects of therapy on concentration of 17-hydrocorticosteroids in the plasma of patients with rheumatic fever, Pediatrics 15: 543 (May) 1955.
- 1855. Seely, J. R., Ely, R. S., Done, A. K., Ainger, L. E., and Kelley, V. C.: Studies of 17-hydroxycorticosteroids. IX. The influence of therapy on adrenal cortical function in patients with rheumatic fever, J. Pediat. 47: 434 (Oct.) 1955.
- 1856. Segal, G., and Kellogg, D. S.: Osteitis condensans ilii, Am. J. Roentgenol. 71: 643 (Apr.) 1954.
- 1857. Segal, S., and Wyngaarden, J. B.: Plasma glutamine and ox/purine content in patients with gout, Proc. Soc. Exper. Biol. and Med. 88: 342 (Mar.) 1955.
- 1858. Segaloff, A.: Cortisone, the triple-edged sword, Ann. Allergy 12: 565 (Sept.-Oct.) 1954.
- 1859. Seifter, J., and Baeder, D. H.: Partially depolymerized hyaluronic acid (PDHA) as a spreading agent, Proc. Soc. Exper. Biol. and Med. 85: 160 (Jan.) 1954.
- 1860. Seifter, J., and Baeder, D. H.: Technical factors influencing permeability of synovial membrane in rabbits, Proc. Soc. Exper. Biol. and Med. 87: 276 (Nov.) 1954.
- 1861. Selinkoff, J. J., and Miller, S. T.: Rheumatic spondylitis in three members of one family, Delaware State M. J. 27: 287 (Nov.) 1955.
- 1862. Selling, L.: Symposium on pain in neck, shoulder and arm. I. Role of pressure on nerve roots and subclavian artery, Portland Clin. Bull. 8: 85 (Mar.) 1955.
- 1863. Selye, H.: An experimental model illustrating the pathogenesis of the diseases of adaptation, J. Clin. Endocrinol. 14: 997 (Sept.) 1954.
- 1864. Selye, H.: On the toxicity of 9a-fluorohydrocortisone and 9a-chlorohydrocortisone, J. Clin. Endocrinol. 15: 384 (Mar.) 1955.
- 1865. Selye, H.: Sketch for a unified theory of medicine, Internat. Rec. Med. 167: 181 (Apr.) 1954.
- 1866. Selve, H.: Stress and disease, Geriatrics 10: 253 (June) 1955.
- 1867. Selye, H.: Stress and disease, Science 122: 625 (Oct.) 1955.
- 1868. Selye, H.: The stress concept in 1955, J. Chron. Dis. 2: 583 (Nov.) 1955.
- 1869. Semmes, R. E., and Murphey, F.: Ruptured intervertebral disks: cervical, thoracic and lumbar, lateral and dentral, S. Clin. North America 34: 1095 (Aug.) 1954.
- 1870. Semple, T., and McCluskie, R. A.: Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma, Brit. M. J. 1: 754 (Mar. 26) 1955.
- 1871. Sengupta, S. R.: Osteoarthritis and its treatment, J. Indian M. A. 24: 579 (May) 1955.
- 1872. Severens, J. M.: Bacteriologic aspects of rheumatic disease, Nebraska M. J. 39: 52 (Feb.) 1954.
- 1873. Sevitt, S.: The diagnosis of synovial tuberculosis of the hand and wrist by epitrochlear gland biopsy, Brit. J. Surg. 41: 375 (Jan.) 1954.
- 1874. Sexton, R. C.: Changing concepts of acute systemic lupus erythematosus, J. Tennessee M. A. 47: 405 (Oct.) 1954.
- 1875. Shackman, N. H., Heffer, E. T., and Kroop, I. G.: The C-reactive protein determination as a measure of rheumatic activity, Am. Heart J. 48: 599 (Oct.) 1954.
- 1876. Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome simulating acute disseminated lupus erythematosus, J. A. M. A. 155: 1492 (Aug. 21) 1954.
- 1877. Shagass, C., and Malmo, R. B.: Psychodynamic themes and localized muscular tension during psychotherapy, Psychosom. Med. 16: 295 (July) 1954.
- 1878. Shapiro, M. J.: Differential diagnosis of rheumatic and non-rheumatic leg-pains. Mod. Concepts Cardiovasc. Dis. 24: 295 (Oct.) 1955.
- 1879. Sharp, J., and Easson, E. C.: Deep x-ray therapy in spondylitis, Brit. M. J. 1: 619 (Mar. 13) 1954.
- 1880. Sharp, J.: Heredo-familial vascular and articular calcification, Ann. Rheumat. Dis. 13: 15 (Mar.) 1954.

- 1881. Shatton, J., and Schubert, M.: Isolation of a mucoprotein from cartilage, J. Biol. Chem. 211: 565 (Dec.) 1954.
- 1882. Shelley, W. B., Harun, J. S., and Pillsbury, D. M.: Treatment of psoriasis and other dermatoses with triamcinolone (Aristocort), J. A. M. A. 167: 959 (June 21) 1958.
- 1883. Shenkin, H. A.: Motorized intermittent traction for treatment of herniated cervical disk, J. A. M. A. 156: 1067 (Nov. 13) 1954.
- 1884. Shephard, E.: Deposit of calcium salts at the wrist, J. Bone and Joint Surg. 37B: 453 (Aug.) 1955.
- 1885. Shepherd, M. M.: A review of 650 hip arthroplasty operations, J. Bone and Joint Surg. 36B: 567 (Nov.) 1954.
- 1886. Sherry, J. B., and Anderson, W.: The natural history of pigmented villonodular synovitis of tendon sheaths, J. Bone and Joint Surg. 37A: 1005 (Oct.) 1955.
- 1887. Shetlar, M. R., Bullock, J. A., Shetlar, C. L., and Payne, R. W.: Comparison of serum C-reactive protein, glycoprotein and seromucoid in cancer, arthritis, tuberculosis and pregnancy, Proc. Soc. Exper. Biol. and Med. 88: 107 (Jan.) 1955.
- 1888. Shetlar, M. R., and Masters, Y. F.: Effect of age on polysaccharide composition of cartilage, Proc. Soc. Exper. Biol. and Med. 90: 31 (Oct.) 1955.
- 1889. Shiers, L. G. P.: Arthroplasty of the knee: preliminary report of a new method, J. Bone and Joint Surg. 36B: 553 (Nov.) 1954.
- 1890. Shoss, M., and Otto, T. G.: Roentgen therapy of subdeltoid tendinitis and bursitis, Missouri Med. 52: 855 (Nov.) 1955.
- 1891. Shriber, W. J.: Rehabilitation of hemiplegic and arthritic patients with physical therapy, M. Clin. North America 39: 1493 (Sept.) 1955.
- 1892. Sicher, H.: Structural and functional basis for disorders of the temporomandibular articulation, J. Oral Surg. 13: 275 (Oct.) 1955.
- 1893. Sickley, J. F., Friedman, I. A., Feldhake, C., and Schwartz, S. O.: In vivo demonstration of the lupus erythematosus phenomenon, J. Lab. and Clin. Med. 46: 624 (Oct.) 1955.
- 1894. Sidell, C. M.: Reiter's syndrome (psoriasis with arthropathy?), Arch. Dermat. and Syph. 71: 774 (June) 1955.
- 1895. Siegal, S.: Allergic reactions to antibiotics, New York State J. Med. 55: 2303 (Aug. 15) 1955.
- 1896. Siekert, R. G., and Clark, E. C.: Neurologic signs and symptoms as early manifestations of systemic lupus erythematosus, Neurology 5: 84 (Feb.) 1955.
- 1897. Sikes, D., Neher, G. M., and Doyle, L. P.: Studies on arthritis in swine. I. Experimental erysipelas and chronic arthritis in swine, Am. J. Vet. Research 16: 349 (July) 1955.
- 1898. Sikes, D., Neher, G. M., and Doyle, L. P.: Studies on arthritis in swine. II. The effects of hormonal therapy on advanced chronic polyarthritis experimentally induced by erysipelothrix infections, Am. J. Vet. Research 16: 367 (July) 1955.
- 1899. Silberberg, M., and Silberberg, R.: Athyroid joint disease in mice of various ages, Arch. Path. 58: 227 (Sept.) 1954.
- 1900. Silberberg, M., Silberberg, R., and Opdyke, M.: Degenerative joint disease in mice bearing anterior hypophyseal, ovarian and adrenal grafts, Endocrinology 54: 26 (Jan.) 1954.
- 1901. Silberberg, M., and Silberberg, R.: Degenerative joint disease of mice as modified by adrenocorticotrophic hormone (ACTH), Exper. Med. and Surg. 13: 279 (Sept.) 1955.
- 1902. Silberberg, M., and Silberberg, R.: Role of thyroid hormone in the pathogenesis of joint disease in mice, effects of radiothyroidectomy and high-fat diets, J. Bone and Joint Surg. 37A: 537 (June) 1955.
- 1903. Silberberg, R., and Silberberg, M.: Degenerative joint disease in ovariectomized mice fed a high-fat diet, Lab. Invest. 3: 228 (May) 1954.

- 1904. Silberberg, R., and Silberberg, M.: Radio-iodine induced athyroid joint disease in mice of different strains, Endocrinology 55: 535 (Nov.) 1954.
- 1905. Silberberg, R., and Silberberg, M.: Skeletal effects of radio-iodine induced thyroid deficiency in mice as influenced by sex, age and strain, Am. J. Anat. 95: 263 (Sept.) 1954
- 1906. Siltzbach, L. E., and Ehrlich, J. C.: The Nickerson-Kveim reaction in sarcoidosis, Am. J. Med. 16: 790 (June) 1954.
- 1907. Silver, M., and Steinbrocker, O.: Resorptive osteopathy in inflammatory arthritis ("absorptive arthritis," "opera glass hand"), Bull. Hosp. Joint Dis. 15: 211 (Oct.)
- 1908. Silverman, F. N.: Calcification of the intervertebral disks in childhood, Radiology 62: 801 (June) 1954.
- 1909. Silverman, J. J., and Berstein, A.: The cardiologist looks at the skin, J. A. M. A. 158: 821 (July 9) 1955.
- 1910. Sime, J. T., and Johnson, B. C.: Metabolism of methionine-C¹⁴H₂ in the chick. II. Distribution of C¹⁴ in the urinary uric acid molecule, J. Biol. Chem. 215: 41 (July) 1955.
- 1911. Simmons, J. L.: ACTH and cortisone in relation to surgery and anesthesia, South. M. J. 47: 362 (Apr.) 1954.
- 1912. Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., v. Euw, J., Schindler, O., and Reichstein, T.: Die Konstitution des Aldosterons. Uber Bestandteile der nebennierenrinde und verwandte Stoffe, Helvet. chim. acta 37: 1200, 1954.
- 1913. Sinex, F. M., and Van Slyke, D. D.: The source and state of the hydroxylysine of collagen, J. Biol. Chem. 216: 245 (Sept.) 1955.
- 1914. Singleton, E. B., and Holt, J. F.: Myositis ossificans progressiva, Radiology 62: 47 (Jan.) 1954.
- 1915. Sinha, R.: Pelvic pain and backache in women, J. Indian M. A. 24: 586 (May) 1955.
- 1916. Sirota, J. H., and Hammerman, D.: Renal function studies in an adult subject with Fanconi syndrome, Am. J. Med. 16: 138 (Jan.) 1954.
- 1917. Sisson, W. R., Jr.: Lateral cervical myelography, New England J. Med. 250: 651 (Apr. 15) 1954.
- 1918. Sissons, H. A., and Hadfield, G. J.: The influence of cortisone on the structure and growth of bone, J. Anat. 89: 69 (Jan.) 1955.
- 1919. Skanse, B.: The effect of cortisone in polymyositis, report of two cases, Acta med. Scandinav. 150: 169, 1954.
- 1920. Skillern, P. G.: Further experiences with blocking of cutaneovisceral reflex arcs for relief of sympatheticotonic states. II. Somatic nerve blocks performed en passant, J. Nerv. and Ment. Dis. 120: 66 (July) 1954.
- 1921. Skillern, P. G.: Suprascapular nerve syndrome as revealed by new (anterior) approach in induction of block, Arch. Neurol. and Psychiat. 71: 185 (Feb.) 1954.
- 1922. Skillicorn, S. A., and Garrity, R. W.: Intracranial Boeck's sarcoid tumor resembling meningioma, J. Neurosurg. 12: 407 (July) 1955.
- 1923. Skillman, R. K., Spurrier, W., Friedman, I. A., and Schwartz, S. O.: Rheumatic fever activity determination by two correlative methods, Arch. Int. Med. 96: 51 (July) 1955.
- 1924. Slack, H. G. B.: Metabolism of elastin in the adult rat, Nature, London 174: 512 (Sept. 11) 1954.
- 1925. Slack, H. G. B.: The metabolism of sulphated polysaccharides in limb atrophy in the rat, Biochem. J. 60: 112 (May) 1955.
- 1926. Slack, H. G. B.: A short review of connective tissue metabolism, Ann. Rheumat. Dis. 14: 238 (Sept.) 1955.
- 1927. Slocumb, C. H.: Rheumatic complaints during chronic hyper-cortisonism and syndromes during withdrawal of cortisone in rheumatic patients, Proc. Staff Meet., Mayo Clin. 28: 655 (Nov. 18) 1953.

- 1928. Slonim, N. B.: Arthralgia, headache, prostration, and fever during hydralazine therapy, J. A. M. A. 154: 1419 (Apr. 24) 1954.
- 1929. Small, J. C., and Small, J. C., Jr.: Treatment of rheumatic disease by desensitization with an aqueous extract of streptococci. I. Fibrositis and hypertrophic arthritis, Ann. Allergy 12: 141 (Mar.) 1954.
- 1930. Small, J. C., and Small, J. C., Jr.: Treatment of rheumatic diseases by desensitization with an aqueous extract of streptococci. II. Rheumatic fever, chorea, and rheumatic carditis, Ann. Allergy 12: 150 (Mar.-Apr.) 1954.
- 1931. Small, J. C., and Small, J. C., Jr.: Treatment of the rheumatic diseases by desensitization with an aqueous extract of streptococci. III. Rheumatoid arthritis, Ann. Allergy 12: 409 (July-Aug.) 1954.
- 1932. Smith, A. D.: The treatment of bone and joint tuberculosis, J. Bone and Joint Surg. 37A: 1214 (Dec.) 1955.
- 1933. Smith, A. M.: Sprain of the pisiform-triquetral joint, J. Bone and Joint Surg. 36B: 618 (Nov.) 1954.
- 1934. Smith, C. F., Pugh, D. G., and Polley, H. F.: Physiologic vertebral ligamentous calcification: an aging process, Am. J. Roentgenol. 74: 1049 (Dec.) 1955.
- 1935. Smith, D. E., and Lewis, Y. S.: Influence of hypophysis and of adrenal cortex upon tissue mast cell of the hamster, Proc. Soc. Exper. Biol. and Med. 88: 631 (Apr.) 1955.
- 1936. Smith, D. E., and Lewis, Y. S.: Influence of hypophysis and adrenal cortex upon tissue mast cell of the rat, Proc. Soc. Exper. Biol. and Med. 87: 515 (Dec.) 1954.
- 1937. Smith, F. B.: Symposium on pain in neck, shoulder and arm. II. Role of common lesions in and about the shoulder joint, Portland Clin. Bull. 8: 101 (Mar.) 1955.
- 1938. Smith, H. D., and Hornisher, C. J.: Ehlers-Danlos syndrome, U. S. Armed Forces M. J. 5: 1672 (Nov.) 1954.
- 1939. Smith, H. G.: Dermatomyositis, a case report with postmortem findings, Brit. M. J. 1: 770 (Mar. 26) 1955.
- 1940. Smith, H. P., and Smith, H. P., Jr.: Ochronosis: report of two cases, Ann. Int. Med. 42: 171 (Jan.) 1955.
- 1941. Smith, J. F.: The kidney in lupus erythematosus, J. Path. and Bact. 70: 41 (July) 1955.
- 1942. Smith, L. W.: Rheumatoid arthritis, evaluation of an embryonic bone marrow malic acid preparation in its treatment—a preliminary report, M. Times, New York 83: 851 (Sept.) 1955.
- 1943. Smith, M. J. H.: The effects of salicylate and adrenocortical preparations added in vitro upon the glycogen content of liver slices, Biochem. J. 59: 52, 1955.
- 1944. Smith, M. J. H., Gray, C. H., and Lunnon, J. B.: Urinary excretion of adrenocortical steroids by patients receiving salicylates, Lancet 1: 1008 (May 15) 1954.
- 1945. Smith, T. L.: The changing number and distribution of the aged population, J. Am. Geriatrics Soc. 3: 1 (Jan.) 1955.
- 1946. Smyth, C. J., Wilson, G. M.; and Huffman, E. R.: Effects of phenylbutazone on serum concentration and renal clearance of urates: a long-term study in gouty and non-gouty arthritics, J. Lab. and Clin. Med. 48: 945 (Dec.) 1956.
- 1947. Smyth, C. J., and Huffman, E. R.: Gouty arthritis—diagnosis and treatment, M. Clin. North America 39: 543 (Mar.) 1955.
- 1948. Smyth, C. J., and Huffman, E. R.: Gouty arthritis—diagnosis and treatment, Rocky Mountain M. J. 52: 513 (June) 1955.
- 1949. Smyth, C. J., and Gum, O. B.: Mast cells in connective tissue diseases, Arthritis and Rheumat. 1: 178 (Apr.) 1958.
- 1950. Snapper, I., and Nathan, D. J.: Formation of large numbers of "lupus cells" from one drop of peripheral blood, J. Invest. Dermat. 24: 473 (Apr.) 1955.
- 1951. Snapper, I., and Nathan, D. J.: The mechanics of the "L. E." cell phenomenon, studied with a simplified test, Blood 10: 718 (July) 1955.

- 1952. Sobel, A. E., and Burger, M.: Calcification. XIV. Investigation of the role of chondroitin sulfate in the calcifying mechanism, Proc. Soc. Exper. Biol. and Med. 87: 7 (Oct.) 1954.
- 1953. Sobel, H., Marmorston, J., and Moore, F. J.: Collagen and hexosamine content of femurs of rats, Proc. Soc. Exper. Biol. and Med. 87: 346 (Nov.) 1954.
- 1954. Sobel, H., and Marmorston, J.: The effect of cortisone on the collagen and hexosamine content of the skin and femurs of one year old rats, Endocrinology 55: 21 (July) 1954.
- 1955. Soffer, L. J., Lundemann, H. H., and Brill, G.: The effect of corticotropin and adrenal steroids on the management of acute disseminated lupus erythematosus, Ann. New York Acad. Sc. 61: 418 (May 27) 1955.
- 1956. Soffer, L. J., Elster, S. K., and Hamerman, D. J.: Treatment of acute disseminated lupus erythematosus with corticotropin and cortisone, Arch. Int. Med. 93: 503 (Apr.) 1954.
- 1957. Sokoloff, L.: Biopsy as a diagnostic procedure in rheumatic diseases, Bull. Rheumat. Dis. 7: (Supp.) S 5 (Oct.) 1956.
- 1958. Sokoloff, L., and Gleason, I. O.: The sternoclavicular articulation in rheumatic diseases, Am. J. Clin. Path. 24: 406 (Apr.) 1954.
- 1959. Sola, A. E., Rodenberger, M. L., and Gettys, B. B.: Incidence of hypersensitive areas in posterior shoulder muscles, a survey of two hundred young adults, Am. J. Phys. Med. 34: 585 (Dec.) 1955.
- 1960. Sola, A. E., and Kuitert, J. H.: Myofascial trigger point pain in the neck and shoulder girdle, Northwest Med. 54: 980 (Sept.) 1955.
- 1961. Solem, J. H., and Römcke, O.: Clinical evaluation of prolonged ACTH and cortisone therapy in 114 cases of rheumatoid arthritis, a 3½-year study, Acta Rheum. Scandinav. 1: 243, 1955.
- 1962. Solem, J. H., Gulbrandsen, R., Römcke, O., and Selás, P.: Experience with the intramuscular, subcutaneous and intravenous administration of ACTH with reference to the development of allergy and resistance, Acta med. Scandinav. 153: 53, 1955.
- 1963. Solem, J. H., and Römcke, O.: Practical considerations in connection with continuous cortico-depot treatment, Acta med. Scandinav. 149: 333, 1954.
- 1964. Solomon, C., Cohn, T. D., and Feldman, F.: Intravenous typhoid vaccine therapy in rheumatic diseases: a correlative study of the stress phenomenon and the clinical results, Am. Pract. and Digest Treat. 5: 769 (Oct.) 1954.
- 1965. Sommerville, J.: Scleroderma and dermatomyositis, Practitioner 173: 151 (Aug.) 1954.
- 1966. Sotelo-Ortiz, F.: Chronic coccidioidal synovitis of the knee joint, J. Bone and Joint Surg. 37A: 49 (Jan.) 1955.
- 1967. Souders, C. R., and Manuell, J. L.: Skeletal deformities in hyperparathyroidism, New England J. Med. 250: 594 (Apr. 8) 1954.
- 1968. Sougin-Mibashan, R., and Horwitz, M.: The uricosuric action of ethyl biscoumacetate, Lancet 1: 1191 (June 11) 1955.
- 1969. Souidan, M. Z. A.: Polyarteritis nodosa and cortisone, J. Kansas M. Soc. 56: 377 (July) 1955.
- 1970. Spence, M. P.: Rheumatoid disease of the lungs and pleura, Arch. Middlesex Hosp. 5: 95 (Apr.) 1955.
- 1971. Spencer, H., Hausinger, A., and Laszlo, D.: The calcium tolerance test in senile osteoporosis, J. Am. Geriatrics Soc. 2: 19 (Jan.) 1954.
- 1972. Sperling, I. L.: Rheumatic diseases, the systemic and intra-synovial use of hydro-cortisone, M. Times, New York 83: 1010 (Oct.) 1955.
- 1973. Sperling, I. L.: Rheumatoid arthritis, indications for the use of cortisone, M. Times, New York 82: 412 (June) 1954.
- 1974. Spies, T. D., Stone, R. E., and Spies, H. A., Jr.: Metacortandracin and delta 1 dehydro-hydrocortisone in rheumatoid arthritis, GP 12: 73 (July) 1955.

- 1975. Spies, T. D., Stone, R. E., Lopez, G. G., Tellechea, C., Toca, R. L., Reboredo, A., and Suarez, R. M.: Prednisone and prednisolone as therapeutic agents, progress report on their integration into general medical practice, J. A. M. A. 159: 645 (Oct. 15) 1955.
- 1976. Spilman, E. L.: Uric acid synthesis in the non-gouty and gouty human, Federation Proc. 13: 302 (Mar.) 1954.
- 1977. Spink, W. W.: Adrenocorticotropic hormone and adrenal steroids in the management of infectious diseases, Ann. Int. Med. 43: 685 (Oct.) 1955.
- 1978. Spink, W. W.: Brucellosis. I. Epidemiology, clinical manifestations and diagnosis. II. Management and prevention, Seminar 16: 8, 1954.
- 1979. Sprague, H. B., and Hardy, H. L.: An unusual case of joint pains and fever, berylliosis and pulmonary hypertension mistaken for rheumatic fever, Circulation 10: 129 (July) 1954.
- 1980. Spring, M.: Swelling of the interphalangeal joints as a manifestation of drug allergy, Ann. Allergy 13: 160 (Mar.-Apr.) 1955.
- 1981. Sproull, D. H.: A peripheral action of sodium salicylate, Brit. J. Pharmacol. 9: 262 (Sept.) 1954.
- 1982. Spurr, C. L., Ford, R. V., Moyer, J. H., Garson, E., and Weller, G.: The effect of probenecid (Benemid) on phosphate excretion and other metabolic processes, Am. J. M. Sc. 228: 256 (Sept.) 1954.
- 1983. Spyropoulos, N. J., Bezos, D. H., and Belka, E.: Treatment of Still's disease with isoniazid, Am. J. Dis. Child. 90: 703 (Dec.) 1955.
- 1984. Stafford, R. O., Barnes, L. E., Bowman, B. J., and Meinzinger, M. M.: Glucocorticoid and mineralocorticoid activities of Δ'-fluorohydrocortisone, Proc. Soc. Exper. Biol. and Med. 89: 371 (July) 1955.
- 1985. Staton, Y. A.: Psychosomatic aspects of the temporomandibular joint syndrome, Arch. Otolaryng. 62: 370 (Oct.) 1955.
- 1986. Stecher, R. M.: Diseases of the bones and joints, Ann. Rev. Med. 6: 243, 1955.
- 1987. Stecher, R. M., and Hersh, A. H.: Familial occurrence of spondylitis, Brit. J. Phys. Med. 18: 176 (Aug.) 1955.
- 1988. Stecher, R. M., and Webster, S. J.: Familial rheumatoid arthritis. Involvement of a woman and her grandmother, Rheumatism 10: 28 (Apr.) 1954.
- 1989. Stecher, R. M.: Herberden's nodes: a clinical description of osteo-arthritis of the finger joints, Ann. Rheumat. Dis. 14: 1 (Mar.) 1955.
- 1990. Stecher, R. M.: Heberden's nodes: concordant osteoarthritis of the fingers in identical twins, Acta Genet. Med. et Gemel. 3: 84. (Jan.) 1954.
- 1991. Stecher, R. M.: Hereditary factors in arthritis, M. Clin. North America 39: 499 (Mar.) 1955.
- 1992. Stecher, R. M.: Heredity of joint diseases, Eugenics Quart. 1: 16 (Mar.) 1954.
- 1993. Stecher, R. M.: Osteoarthritis, Missouri Med. 51: 998 (Dec.) 1954.
- 1994. Stecher, R. M., and Hauser, H.: Traumatic Heberden's nodes: osteoarthritis of the fingers due to injury, Am. J. Roentgenol. 72: 452 (Sept.) 1954.
- 1995. Steel, S. J., and Moffatt, J. L.: Stevens-Johnson syndrome and granulocytopenia after phenylbutazone, Brit. M. J. 1: 795 (Apr. 3) 1954.
- 1996. Stefanini, M., and Mednicoff, I. B.: Demonstration of antivessel agents in serum of patients with anaphylactoid purpura and periarteritis nodosa, J. Clin, Investigation 33: 967 (June) 1954.
- 1997. Stein, I., and Beller, M. L.: The orthopedic management of rheumatoid arthritis, J. Albert Einstein M. Center 4: 28 (Nov.) 1955.
- 1998. Stein, T.: Fatal agranulocytosis following phenylbutazone (Butazolidin) therapy, J. M. A. Alabama 24: 87 (Oct.) 1954.
- 1999. Steinberg, C. L., Gardner, D. E., Smith, F. A., and Hodge, H. C.: Comparison of rheumatoid (ankylosing) spondylitis and crippling fluorosis, Ann. Rheumat. Dis. 14: 378 (Dec.) 1955.

- 2000. Steinbrocker, O., Neustadt, D. H., and Ehrlich, M.: Butazolidin in the treatment of gout, with a comparison with other agents, M. Clin. North America 38: 611 (Mar.) 1954.
- Steinbrocker, O., Neustadt, D., and Bosch, S. J.: Painful shoulder syndromes, their diagnosis and treatment, M. Clin. North America 39: 563 (Mar.) 1955.
- 2002. Steinbrocker, O., and Neustadt, D.: Psychogenic rheumatism, some special diagnostic and therapeutic considerations, Missouri Med. 51: 996 (Dec.) 1954.
- 2003. Steinbrocker, O., Friedman, H. H., and Lapin, L.: The shoulder-hand syndrome, Postgrad. Med. 16: 46 (July) 1954.
- 2004. Stephens, H., and Janus, W. L.: Dysphagia of transitory type produced by hyper-trophic spurs on cervical vertebrae, Ann. Int. Med. 41: 823 (Oct.) 1954.
- 2005. Stephenson, W. H.: The management of ankylosing spondylitis, Physiotherapy 41: 109 (Apr.) 1955.
- 2006. Stern, W. E.: The lumbar intervertebral disc disease syndrome, clinical correlation of one hundred and seventy-five cases, West. J. Surg. 63: 647 (Oct.) 1955.
- 2007. Stern, W. E., and Rand, R. W.: Spinal cord dysfunction from cervical intervertebral disk disease, Neurology 4: 883 (Dec.) 1954.
- 2008. Stetson, C. A., Jr.: The relation of antibody response to rheumatic fever, Chap. 15 of Streptococcal infections, edited by M. McCarty, 1954, Columbia University Press, New York.
- 2009. Stetten, D., Jr.: Recent contributions to the understanding of the metabolic defect in gout, Geriatrics 9: 163 (Apr.) 1954.
- 2010. Stevenson, F. H.: The chemotherapy of orthopaedic tuberculosis, J. Bone and Joint Surg. 36B: 5 (Feb.) 1954.
- Stevenson, F. H.: The natural history of pleural effusion and orthopaedic tuberculosis,
 J. Bone and Joint Surg. 37B: 80 (Feb.) 1955.
- Stiebel, P.: Impressions of work with Canadian Arthritis and Rheumatism Society.
 How Canada is fighting her No. 1 crippler—arthritis, Physiotherapy 41: 216 (July) 1955.
- 2013. Stillman, J. S.: The treatment of osteoarthritis, M. Clin. North America 38: 1475 (Sept.) 1954.
- 2014. Stinchfield, F. E., and Sinton, W. A.: Clinical significance of the transitional lumbosacral vertebra, J. A. M. A. 157: 1107 (Mar. 26) 1955.
- 2015. Stoddard, A.: Adhesive capsulitis of the shoulder and the sedimentation rate, Brit. J. Phys. Med. 18: 9 (Jan.) 1955.
- 2016. Stoddard, A.: Traction for cervical nerve root irritation, Physiotherapy 40: 48 (Feb.) 1954.
- Stoffyn, P. J., and Jeanloz, R. W.: Identification of amino sugars by paper chromatography, Arch. Biochem. 52: 373 (Oct.) 1954.
- 2018. Stoikovic, J. P., Bonfiglio, M., and Paul, W. D.: Myositis ossificans complicating poliomyelitis, Arch. Phys. Med. 36: 236 (Apr.) 1955.
- 2019. Stokes, E. J.: Human infection with pleuropneumonia-like organisms, Lancet 1: 276 (Feb. 5) 1955.
- 2020. Stoll, B. A., and Beetham, W. R.: Undigital clubbing, with report of a case, M. J. Australia 2: 852 (Nov. 27) 1954.
- 2021. Stollerman, G. H., Glick, S. J., and Anderson, H. C.: Effect of adrenocortical hormones on presence of C-reactive protein in blood, Proc. Soc. Exper. Biol. and Med. 87: 241 (Oct.) 1954.
- 2022. Stollerman, G. H.: Potentialities for and limitations in the control of chronic rheumatic fever by prophylactic measures, J. Chron. Dis. 1: 216 (Feb.) 1955.
- 2023. Stollerman, G. H.: Prevention of rheumatic fever, Am. Pract. and Digest Treat. 5: 589 (Aug.) 1954.
- 2024. Stollerman, G. H.: The prevention of rheumatic fever by the use of antibiotics, Bull. New York Acad. Med. 31: 165 (Mar.) 1955.

- 2025. Stollerman, G. H., Rusoff, J. H., and Hirschfeld, I.: Prophylaxis against group A streptococci in rheumatic fever, New England J. Med. 252: 787 (May 12) 1955.
- 2026. Stollerman, G. H., Lewis, A. J., Schultz, I., and Taranta, A.: Relationship of immune response to group A streptococci to the course of acute chronic and recurrent rheumatic fever, Am. J. Med. 20: 163 (Feb.) 1956.
- 2027. Stollerman, G. H.: Repository benzathine penicillin for the control of rheumatic fever, Bull. Rheumat. Dis. 5: 79 (Dec.) 1954.
- 2028. Stollerman, G. H.: The use of antibiotics for the prevention of rheumatic fever, Am. J. Med. 17: 757 (Dec.) 1954.
- 2029. Stolzer, B. L., Houser, H. B., and Clark, E. J.: Comparative effects of aspirin, ACTH, and cortisone on the antistreptolysin "O" titer and gamma globulin concentration in rheumatic fever, J. Lab. and Clin. Med. 44: 229 (Aug.) 1954.
- 2030. Stolzer, B. L., Houser, H. B., and Clark, E. J.: Therapeutic agents in rheumatic carditis, effects of acetylsalicylic acid, corticotropin, and cortisone, Arch. Int. Med. 95: 677 (May) 1955.
- 2031. Storey, G., and Tegner, W. S.: Paraplegic para-articular calcification, Ann. Rheumat. Dis. 14: 176 (June) 1955.
- 2032. Stoughton, R. B.: Treatment of chronic lupus erythematosus with Atabrine and chloroquine, Illinois M. J. 107: 299 (June) 1955.
- 2033. Stowell, A., Hayne, R. A., and Martini, R. F.: The diagnosis and evaluation of treatment of the lumbar intervertebral disk, J. Oklahoma M. A. 47: 15 (Jan.) 1954.
- 2034. Strickland, B.: Pulmonary appearances in polyarteritis nodosa, J. Fac. Radiol., London 6: 201 (Jan.) 1955.
- 2035. Strully, K. J., and Heiser, S.: Lumbar and sacral cysts of meningeal origin, Radiology 62: 544 (Apr.) 1954.
- 2036. Sümegi, I., Goreczky, L., and Róth, I.: Connective tissue and amyloid, Acta Morphol. Hung. 4: 130, 1954.
- 2037. Sullivan, J. D.: Psychiatric factors in low back pain, New York State J. Med. 55: 227 (Jan. 15) 1955.
- 2038. Sundblad, L., Egelius, N., and Jonsson, E.: Action of hydrocortisone on the hyaluronic acid of joint fluids in rheumatoid arthritis, Scandinav. J. Clin. and Lab. Invest. 6: 295, 1954.
- 2039. Sundblad, L.: Determination of anomalous viscosity in pathological joint fluids, Scandinav. J. Clin. and Lab. Invest. 6: 288, 1954.
- 2040. Sundt, P. E.: Psychogenic rheumatism, Proc. Roy. Soc. Med. 48: 66 (Feb.) 1955.
- 2041. Surdakowski, A. Z.: Periarteritis nodosa due to penicillin, New York State J. Med. 54: 388 (Feb.) 1954.
- 2042. Susinno, A. M., and Verdon, R. E.: Results of treatment of calcific tendinitis with adenosine 5-monophosphate: preliminary report, J. A. M. A. 154: 239 (Jan. 16) 1954.
- 2043. Svaar, O.: Experiences in surgical treatment of lumbar disk herniation, Acta chir. Scandinav. 109: 97, 1955.
- 2044. Svartz, N., and Schlossmann, K.: Cold precipitable haemagglutinating factor in serum from patients with rheumatoid arthritis, Ann. Rheumat. Dis. 14: 191 (June) 1955.
- 2045. Svartz, N., and Schlossmann, K.: A serum cold precipitable hemagglutinating factor in rheumatoid arthritis, Acta med. Scandinav. 149: 83, 1954.
- 2046. Svien, H. J., Ivins, J. C., and Cooney, J. F.: Anterior decompression of the spinal cord for paraplegia associated with Pott's disease: report of case, Proc. Staff Meet., Mayo Clin. 29: 326 (June 2) 1954.
- 2047. Svien, H. J., and Karavitis, A. L.: Multiple protrusions of intervertebral disks in the upper thoracic region: report of case, Proc. Staff Meet., Mayo Clin. 29: 375 (June 30) 1954.
- 2048. Swan, D. M.: Shoulder-hand syndrome following hemiplegia, Neurology 4: 480 (June) 1954.

- 2049. Swanson, J. N.: A five year review of the treatment of rheumatoid arthritis and ankylosing spondylitis with steroid hormones, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 83.
- 2050. Swingle, W. W., Baker, C., Eisler, M., LeBrie, S. J., and Brannick, L. J.: Efficacy of 9 alpha-halo adrenal steroids for maintenance of adrenalectomized dogs. Proc. Soc. Exper. Biol. and Med. 88: 193 (Feb.) 1955.
- 2051. Swingle, W. W., Baker, C., Eisler, M., LeBrie, S. J., and Brannick, L.: Maintenance of adrenal ectomized dogs with 9 alpha-halo adrenal and other steroids, Endocrinology 57: 220 (Aug.) 1955.
- 2052. Swirsky, M. Y., and Lowman, R. M.: Sarcoidosis in siblings, New England J. Med. 252: 476 (Mar. 24) 1955.
- 2053. Sylvén, B., and Ambrose, E. J.: Birefringent fibres of hyaluronic acid, Biochim. et Biophys. Acta 18: 587 (Dec.) 1955.
- Talbott, J. H.: Acute dermatomyositis and generalized scleroderma (systemic scleroderma), Seminar 17: 18, 1955.
- 2055. Talbott, J. H.: Gout, J. Chron. Dis. 1: 338 (Mar.) 1955.
- 2056. Talbott, J. H.: Gout and gouty arthritis, Nursing Outlook 2: 540 (Oct.) 1954.
- 2057. Talbott, J. H.: Gout becomes of age, Ann. Int. Med. 42: 1137 (May) 1955.
- 2058. Talbott, J. H.: Gout, the pathogenesis and treatment, Seminar Rep. 1: 2, 1956.
- 2059. Talbott, J. H.: The metabolic defect of gout, M. Clin. North America 39: 529 (Mar.) 1955.
- 2060. Talbott, J. H., and Lockie, L. M.: The treatment of gout, Geriatrics 8: 599 (Dec.) 1953.
- 2061. Talbott, J. H.: The use of ACTH, cortisone, and phenylbutazone, New York State J. Med. 54: 365 (Feb. 1) 1954.
- 2062. Tapiovaara, J., and Heinivaara, O.: Correlation of cervico-brachialgias and roentgeno-logical findings in the cervical spine, Ann. chir. et gynaec. Fenniae 43 Supp. 5: 436, 1954.
- 2063. Taran, L. M., and Szilagyi, N.: The determination of the QTc, Bull. St. Francis Hosp. and Sanit. 11: 19 (Oct.) 1954.
- 2064. Taran, L. M., Gulotta, G. A., Chand, D., and Angelos, P. H.: The effect of cortisone and ACTH on protracted rheumatic carditis in children, Bull. St. Francis Hosp. and Sanit. 11: 1 (Jan.) 1954.
- 2065. Taranta, A., and Stollerman, G. H.: The relationship of Sydenham's chorea to infection with group A streptococci, Am. J. Med. 20: 170 (Feb.) 1956.
- 2066. Taubenhaus, M., Eisenstein, B., and Pick, A.: Cardiovascular manifestations of collagen diseases, Circulation 12: 903 (Nov.) 1955.
- 2067. Taverner, D.: Muscle spasm as a cause of somatic pain, Ann. Rheumat. Dis. 13: 331 (Dec.) 1954.
- 2068. Taylor, A. R.: Pain associated with cervical spondylosis, Rheumatism 10: 52 (July) 1954.
- 2069. Taylor, H. W. Y., King, J. B., and Stecher, R. M.: Osteoarthritis of the hip in gorillas, Clin. Orthop. 6: 149, 1955.
- 2070. Tedeschi, C. G., Wagner, B. M., and Pani, K. C.: Studies in rheumatic fever. I. Clinical significance of the Aschoff body based on morphologic observations, Arch. Path. 60: 408 (Oct.) 1955.
- Tegner, W.: Physical methods in the treatment of rheumatic disorders, Post-Grad. M. J. 31: 632 (Dec.) 1955.
- 2072. Tegner, W.: Psychogenic rheumatism, Proc. Roy. Soc. Med. 48: 69 (Feb.) 1955.
- 2073. Teilum, G., and Lindahl, A.: Frequency and significance of amyloid changes in rheumatoid arthritis, Acta med. Scandinav. 149: 449, 1954.
- 2074. Teilum, G.: Studies on pathogenesis of amyloidosis. II. Effect of nitrogen mustard in inducing amyloidosis, J. Lab. and Clin. Med. 43: 367 (Mar.) 1954.

- 2075. Telkkä, A., and Kulonen, E.: On the effect of acid extraction and hyaluronidase treatment of collagen on its standard stainings, Acta path. et microbiol. Scandinav. 35: 469, 1954.
- 2076. Tenney, S. M., and Miller, R. M.: The respiratory and circulatory actions of salicylate, Am. J. Med. 19: 498 (Oct.) 1955.
- 2077. Tess, B.: Fibrositis, Medicine Illus. (London) 9: 600 (Sept.) 1955.
- 2078. Thamdrup, E.: A case of arthrogryposis multiplex congenita, Acta pædiat. 44: 95 (Jan.) 1955.
- 2079. Thiemeyer, J. S., Jr.: Chondromalacia of the patella, Virginia M. Monthly 82: 225 (May) 1955.
- 2080. Thiemeyer, J. S., Jr.: Monarticular coccidioidal arthritis: report of a case with apparent cure following synovectomy, J. Bone and Joint Surg. 36A: 387 (Apr.) 1954.
- 2081. Thomas, A. E.: Chronic arthritis after recurrent rheumatic fever, Ann. Rheumat. Dis. 14: 259 (Sept.) 1955.
- 2082. Thomas, D. P. P., and Dingle, J. T. M.: Serum antiplasmin and plasmin in rheumatoid arthritis, Ann. Rheumat. Dis. 14: 195 (June) 1955.
- 2083. Thomas, D. P. P., and Dingle, J. T. M.: In vitro studies of rheumatoid synovium. Preliminary metabolic comparison between synovial membrane and villi, Brit. J. Exper. Path. 36: 195 (Apr.) 1955.
- 2084. Thomas, L.: Cortisone, ACTH and infection, Bull. New York Acad. Med. 31: 485 (July) 1955.
- 2085. Thomas, L., Smith, R. T., and von Korff, R.: Studies on the generalized Shwartzman reaction. VII. The role of fibrinogen in the deposition of fibrinoid after combined injections of endotoxin and synthetic acidic polymer, J. Exper. Med. 102: 263 (Sept.) 1955.
- 2086. Thompson, A. R.: Industry's contribution in the field of rehabilitation, Bull. World Health Organ. 13: 635, 1955.
- 2087. Thompson, M.: Osteitis condensans ilii and its differentiation from ankylosing spondylitis, Ann. Rheumat. Dis. 13: 147 (June) 1954.
- 2088. Thompson, M., Sinclair, R. J. G., and Duthie, J. J. R.: Thrombocytopenic purpura after administration of gold, comparison of treatment with dimercaprol, A.C.T.H. and cortisone, Brit. M. J. 1: 899 (Apr. 17) 1954.
- 2089. Thompson, M. S., and Dickinson, P. H.: Osgood-Schlatter's disease in the Army, J. Internat. Coll. Surgeons 23: 170 (Feb.) 1955.
- 2090. Thorn, G. W., Laidlaw, J. C., Renold, A. E., and Reddy, W. J.: The adrenals—1854–1954, Canad. M. A. J. 72: 883 (June 15) 1955.
- 2091. Thorn, G. W., Renold, A. E., Morse, W. I., Goldfien, A., and Reddy, W. J.: Highly potent adrenal cortical steroids: structure and biologic activity, Ann. Int. Med. 43: 979 (Nov.) 1955.
- 2092. Thulin, K. E.: The reaction of streptococcal agglutination relative to the Ras factor in rheumatoid arthritis; Acta Rheum. Scandinav. 1: 22, 1955.
- 2093. Thune, S., and Truedsson, E.: The effect of serum and certain electrolytes on the activity of testis hyaluronidase in carbonic acid-bicarbonate buffer pH 7.4¹, Acta Rheum. Scandinav. 1: 47, 1955.
- 2094. Tidwell, R. A.: Rheumatic fever prophylaxis, Northwest Med. 53: 470 (May) 1954.
- 2095. Tidwell, R. A.: The single approach to streptococcic prophylaxis, Northwest Med 54: 467 (May) 1955.
- 2096. Tillis, H. H., and Goldman, L. M.: Hematological findings in the treatment of rheumatoid disease with Meticorten, J. Newark Beth Israel Hosp. 6: 255 (July) 1955.
- 2097. Tillson, E. K., Schuchardt, G. S., Fishman, J. K., and Beyer, K. H.: The determination of probenecid (Benemid) in body fluids, J. Pharmacol. and Exper. Therap. 111: 385 (Aug.) 1954.

- 2098. Törnblom, N.: Adrenals and serum polysaccharides. I. Action of ACTH on the serum polysaccharides in rabbit, Acta med. Scandinav. 153: 143, 1955.
- 2099. Törnblom, N.: Adrenals and serum polysaccharides. II. Action of DDD on the serum polysaccharides in rabbit, Acta med. Scandinav. 153: 149, 1955.
- 2100. Toland, J. J., 3rd: Spondylolisthesis in identical twins, Clin. Orthop. 5: 184, 1955.
- 2101. Toone, E. C., Jr., and Irby, R.: Effect of cortisone in the long-term treatment of rheumatoid arthritis, Am. J. Med. 18: 41 (Jan.) 1955.
- 2102. Toone, E. C., Jr., and Irby, W. R.: Evaluation of phenylbutazone (Butazolidin) in the treatment of rheumatoid spondylitis: report of 50 cases, Ann. Int. Med. 41: 70 (July) 1954.
- 2103. Toone, E. C., Jr., and Kawchak, J.: Painful non-arthritic disturbances of the hand and wrist, Virginia M. Monthly 82: 441 (Oct.) 1955.
- 2104. Toone, E. C., Jr.: Phenylbutazone (Butazolidin), Bull. Rheumat. Dis. 5: 83 (Feb.) 1955.
- 2105. Tophøj, E., Bastrup-Madsen, P., and Bechgaard, P.: Phenylbutazone in small doses in the treatment of joint diseases, Acta med. Scandinav. 152: 153, 1955.
- 2106. Townsend-Coles, W. F.: A report of seven cases of chondro-osteo-dystrophy (Morquio's disease) Arch. Dis. Childhood 29: 7 (Feb.) 1954.
- 2107. Tragerman, L. J., and Corley, C. L.: Rheumatic lesions in left atrial appendages, pathologic studies of material removed during mitral commissurotomy, California Med. 82: 163 (Mar.) 1955.
- 2108. Traut, E. F.: Specific vascular changes in gout, J. A. M. A. 156: 591 (Oct. 9) 1954.
- 2109. Travell, J.: Referred pain from skeletal muscle, the pectoralis major syndrome of breast pain and soreness and the sternomastoid syndrome of headache and dizziness, New York State J. Med. 55: 331 (Feb. 1) 1955.
- 2110. Trevathan, R. D., and Tatum, J. C.: Rarity of concurrence of psychosis and rheumatoid arthritis in individual patients, J. Nerv. and Ment. Dis. 120: 83 (July) 1954.
- 2111. Trommer, P. R., Gellman, M. B., Smith, R. T., Hollander, J. L., and Maguire, E. F.: The treatment of rheumatoid arthritis, J. Am. M. Women's A. 9: 205 (July) 1954.
- 2112. Trowbridge, W. V., and French, J. D.: The "false positive" lumbar myelogram, Neurology 4: 339 (May) 1954.
- 2113. Trueta, J.: Osteoarthritis of the hip, Ann. Roy. Coll. Surgeons, England 15: 174 (Sept.) 1954.
- 2114. Tubiana, R.: Prognosis and treatment of Dupuytren's contracture, J. Bone and Joint Surg. 37A: 1155 (Dec.) 1955.
- 2115. Tumulty, P. A.: The clinical course of systemic lupus erythematosus, J. A. M. A. 156: 947 (Nov. 6) 1954.
- 2116. Turek, S. L.: The painful and stiff shoulder, a plan of treatment based on known and theoretical factors; plea for standardization in evaluation of results, J. Internat. Coll. Surgeons 22: 695 (Dec.) 1954.
- 2117. Turner, L. W., and Lansbury, J.: Low diastolic pressure as a clinical feature of rheumatoid arthritis and its possible etiologic significance, Am. J. M. Sc. 227: 503 (May) 1954.
- 2118. Turner, S. J., LeVine, L., and Rothman, A.: Lupus erythematosus and pregnancy, Am. J. Obst. and Gynec. 70: 102 (July) 1955.
- 2119. Tyler, F. H., Eik-nes, K., Sandberg, A. A., Florentin, A. A., and Samuels, L. T.: Adrenocortical capacity and the metabolism of cortisol in elderly patients, J. Am. Geriatrics Soc. 3: 79 (Feb.) 1955.
- 2120. Ungerleider, H. E.: The internist and life insurance, Ann. Int. Med. 41: 124 (July) 1954.
- 2121. Upton, A. C., and Gude, W. D.: Physiologic and histochemical changes in connective tissue of rat induced by total body irradiation, Arch. Path. 58: 258 (Sept.) 1954.

- 2122. Urteaga, O., Larrea, P., and Calderon, J.: Erythromycin in human brucellosis, Anti-biotic Med. 1: 513 (Sept.) 1955.
- 2123. Uzman, L. L.: Chemical nature of the storage substance in gargoylism, Arch. Path. 60: 308 (Sept.) 1955.
- 2124. Vaillancourt, de G.: The cutaneous application of a nicotinic acid cream as a diagnostic aid in various rheumatic diseases, Canad. M. A. J. 71: 283 (Sept.) 1954.
- 2125. Vaillancourt, de G., and Adamkiewicz, L.: The cutaneous application of a nicotinic acid cream as a diagnostic aid in various rheumatic diseases, First Canadian Conference on Research in Rheumatic Diseases, Toronto, March, 1955, p. 49.
- 2126. Valobra, G.: Ultrasonic therapy for prolapsed intervertebral discs, Brit. J. Phys. Med. 17: 109 (May) 1954.
- 2127. Van Allen, M. W.: Herniated lumbar intervertebral discs: diagnosis and management, Mississippi Valley M. J. 76: 130 (May) 1954.
- 2128. Van Demark, R. E., and Mitchell, C. B.: Diffuse synovial osteochondromatosis of knee: case with removal of 439 loose bodies and synovectomy, South Dakota J. Med. and Pharm. 8: 181 (June) 1955.
- 2129. Van Der Veen, J.: A rapid and simple method for conducting large series of complement fixation tests and antistreptolysin "O" titrations, J. Lab. and Clin. Med. 45: 323 (Feb.) 1955.
- 2130. Van Landingham, J. H.: Herniation of thoracic intervertebral discs with spinal cord compression in kyphosis dorsalis juvenilis (Scheuermann's disease), case report, J. Neurosurg. 11: 327 (May) 1954.
- 2131. Van Leeuwen, G. J., Kelly, H. G., and Jackson, R. L.: Corticotropin and cortisone in rheumatic fever, preliminary report of the effect on the electrophoretic patterns of plasma or serum proteins of children, Am. J. Dis. Child. 89: 304 (Mar.) 1955.
- 2132. Van Leeuwen, G. J., Kelly, H. G., and Jackson, R. L.: Preliminary report of the effect of corticotropin (ACTH) and cortisone on the electrophoretic patterns of plasma or serum proteins of children with rheumatic fever, J. Lab. and Clin. Med. 44: 943 (Dec.) 1954.
- 2133. Van Slyck, E. J.: Pancytopenia associated with rheumatoid arthritis—Felty's syndrome treatment with cortisone and splenectomy, J. Michigan M. Soc. 53: 735 (July) 1954.
- 2134. Van Swaay, H.: Aplastic anaemia and myeloid leukaemia after irradiation of the vertebral column, Lancet 2: 225 (July 30) 1955.
- 2135. Vander Laan, W. P.: Flexion deformities in adrenal insufficiency, J. Clin. Investigation 34: 968 (June) 1955.
- 2136. Variava, N. S.: Painful musculoskeletal conditions and their treatment with pyrazolones, J. Indian M. A. 23: 499 (Aug.) 1954.
- 2137. Vaughan, J. H., Armato, A., Goldthwait, J. C., Brachman, P., Favour, C. B., and Bayles, T. B.: A study of gamma globulin in rheumatoid arthritis, J. Clin. Investigation 34: 75 (Jan.) 1955.
- 2138. Vaux, D. M.: Malignant synovioma, J. Indian M. A. 23: 345 (May) 1954.
- 2139. Verbiest, H.: Further experiences on the pathological influence of a developmental narrowness of the bony lumbar vertebral canal, J. Bone and Joint Surg. 37B: 576 (Nov.) 1955.
- 2140. Verbiest, H.: A radicular syndrome from developmental narrowing of the lumbar vertebral canal, J. Bone and Joint Surg. 36B: 230 (May) 1954.
- 2141. Verloop, M. C.: Some observations concerning the L. E. phenomenon, Acta med. Scandinav. 148: 183, 1954.
- 2142. Viani, H.: Butazolidin in the treatment of psoriasis, J. Irish M. A. 37: 345 (Nov.) 1955.
- 2143. Villa, L., Ballabio, C. B., and Sala, G.: Metacortandracin and 9-alpha-fluoro hydrocortisone acetate in rheumatic diseases, Ann. Rheumat. Dis. 14: 251 (Sept.) 1955.

- 2144. Villarreal, R., Ganong, W. F., and Gray, S. J.: Effect of adrenocorticotrophic hormone upon the gastric secretion of hydrochloric acid, pepsin and electrolytes in the dog, Am. J. Physiol. 183: 485 (Dec.) 1955.
- 2145. Vivian, D. N., Weed, L. A., McDonald, J. R., Clagett, O. T., and Hodgson, C. H.: Histoplasmosis: clinical and pathologic study of 20 cases, Surg., Gynec. and Obst. 99: 53 (July) 1954.
- 2146. Vogl, A., Blumenfeld, S., and Gutner, L. B.: Diagnostic significance of pulmonary hypertrophic osteoarthropathy, Am. J. Med. 18: 51 (Jan.) 1955.
- 2147. Volpe, R., and Ogryzlo, M. A.: The cryoglobulin inclusion cell, Blood 10: 493 (May) 1955.
- 2148. Von Werssowitz, O. F.: Biophysical principles in selection of hand splints, Am. J. Occup. Therapy 9: 59 (Mar./Apr.) 1955.
- 2149. Wager, O.: Serological reactions in rheumatoid arthritis, the relation of the agglutination activating factor (AAF) to complement, Ann. med. exper. et biol. Fenniae 33: 291, 1955.
- 2150. Wagner, B. M.: Histochemical studies of fibrinoid substances and other abnormal tissue proteins. II. Effect of fibrinolytic enzymes, Arch. Path. 59: 63 (Jan.) 1955.
- 2151. Wagner, B. M.: Histochemical studies of fibrinoid substances and other abnormal tissue proteins. IV. Protein character of amyloid, Arch. Path. 60: 221 (Aug.) 1955.
- 2152. Wagner, B. M., and Tedeschi, C. G.: Studies in rheumatic fever. II. Origin of cardiac giant cells, Arch. Path. 60: 423 (Oct.) 1955.
- 2153. Wagner, V., and Rejholec, V.: Agglutinins and incomplete antibodies after a single antigenic inoculation in normal and rheumatic individuals, Ann. Rheumat. Dis. 14: 243 (Sept.) 1955.
- 2154. Waine, H.: American Rheumatism Association interim session at Bethesda, Bull. Rheumat. Dis. 5: 81 (Jan.) 1955.
- 2155. Waine, H.: Review of rheumatic diseases, Arch. Int. Med. 93: 121 (Jan.) 1954.
- 2156. Walchef, L. S.: The traction brace, a new traction method in the conservative treatment of intervertebral disc lesions, Surgery 35: 758 (May) 1954.
- 2157. Wald, N., and Kissin, M.: Familial hereditary purpura simplex with Schönlein-Henoch syndrome, response to corticotropin (ACTH), cortisone, and antihistaminics, J. A. M. A. 159: 29 (Sept. 3) 1955.
- 2158. Walker, C. S.: Calcification of intervertebral discs in children, J. Bone and Joint Surg. 36B: 601 (Nov.) 1954.
- 2159. Walker, O. R., and Hall, R. H.: Coccidioidal tenosynovitis: report of a case, J. Bone and Joint Surg. 36A: 391 (Apr.) 1954.
- 2160. Wallace, H.: Connective tissue disease (collagen disease), Proc. Roy. Soc. Med. 48: 559 (July) 1955.
- 2161. Wallace, H. M., and Rich, H.: Changing status of rheumatic fever and rheumatic heart disease in children and youth, Am. J. Dis. Child. 89: 7 (Jan.) 1955.
- 2162. Wallis, A. D., and Viergiver, E.: The relation of the serum inhibitor of serum-extracted streptolysin S to serum phospholipid from the standpoint of rheumatic fever, Am. J. M. Sc. 227: 431 (Apr.) 1954.
- 2163. Wallis, A. D., and Viergiver, E.: Serum phospholipid and rheumatic fever, Am. J. M. Sc. 227: 171 (Feb.) 1954.
- 2164. Wang, P., Glass, H. L., Goldenberg, L., Stearns, G., Kelly, H. G., and Jackson, R. L.: Serum vitamin A and carotene levels in children with rheumatic fever, Am. J. Dis. Child. 87: 659 (June) 1954.
- 2165. Wannamaker, L. W.: Control of group A streptococcal infections and their sequelae, Journal Lancet 75: 197 (May) 1955.
- 2166. Wannamaker, L. W.: The epidemiology of streptococcal infections, Chap. 12 of Streptococcal infections, edited by M. McCarty, 1954, Columbia University Press, New York.

- 2167. Ward, L. E., Polley, H. F., Slocumb, C. H., Hench, P. S., Mason, H. L., and Mattox, V. R.: Clinical and metabolic effects of aldosterone in rheumatoid arthritis, J. Lab. and Clin. Med. 44: 948 (Dec.) 1954.
- 2168. Ward, L. E., Polley, H. F., Slocumb, C. H., Hench, P. S., Mason, H. L., Mattox, V. R., and Power, M. H.: The effects of aldosterone (Electrocortin) and of 9a-fluorohydrocortisone acetate on rheumatoid arthritis: preliminary report, Proc. Staff Meet., Mayo Clin. 29: 649 (Dec. 22) 1954.
- 2169. Ward, L. E., and Hench, P. S.: Effects of aldosterone (Electrocortin), 9 alpha-fluorohydrocortisone acetate, and 1-dehydrocortisone (Metacortandracin) in rheumatoid arthritis, Ann. New York Acad. Sc. 61: 620 (May 27) 1955.
- 2170. Ward, L. E.: Precautions in the use of cortisone for treatment of rheumatic diseases, Minnesota Med. 38: 304 (May) 1955.
- 2171. Warner, A. H.: Aptyalism due to intoxication with phenylbutazone (Butazolidin), Arch. Otolaryng. 62: 308 (Sept.) 1955.
- 2172. Warter, P. J.: Diagnosis and treatment in rheumatoid arthritis, Delaware State M. J. 27: 53 (Mar.) 1955.
- 2173. Wasserman, E.: Weber-Christian disease, Am. Pract. and Digest Treat. 6: 1169 (Aug.) 1955.
- 2174. Wassmann, K.: Osteitis condensans ilii, Acta med. Scandinav. 151: 151, 1955.
- 2175. Watkins, A. L.: Physical medicine and rehabilitation in the management of hip disabilities, Arch. Phys. Med. 35: 747 (Dec.) 1954.
- 2176. Wawzonek, S., Ponseti, I. V., Shepard, R. S., and Wiedenmann, L. G.: Epiphyseal plate lesions, degenerative arthritis, and dissecting aneurysm of the aorta produced by aminonitriles, Science 121: 63 (Jan. 14) 1955.
- 2177. Wayne, E. J.: The dangers and complications of cortisone and corticotrophin therapy, Practitioner 175: 546 (Nov.) 1955.
- 2178. Webb, J. H., Svien, H. J., and Kennedy, R. L. J.: Protruded lumbar intervertebral disks in children, J. A. M. A. 154: 1153 (Apr. 3) 1954.
- 2179. Weckesser, E. C.: Congenital flexion-adduction deformity of the thumb (congenital "clasped thumb"), J. Bone and Joint Surg. 37A: 977 (Oct.) 1955.
- 2180. Wedgwood, R. J. P., and Klaus, M. H.: Anaphylactoid purpura (Schönlein-Henoch syndrome)—a long-term follow-up study with special reference to renal involvement, Pediatrics 16: 196 (Aug.) 1955.
- 2181. Wedum, B. G., and Rhodes, P. H.: Differential diagnosis of rheumatic fever in office practice, J. A. M. A. 157: 981 (Mar. 19) 1955.
- 2182. Wegelius, O., and Hjelmman, G.: Vital staining of mast cells and fibrocytes, Acta path. et microbiol. Scandinav. 36: 304, 1955.
- 2183. Wegman, M. E.: Some international aspects of rheumatic fever, Pediatrics 15: 627 (May) 1955.
- 2184. Wehrmacher, W. H.: Significance of Tietze's syndrome in differential diagnosis of chest pain, J. A. M. A. 157: 505 (Feb. 5) 1955.
- 2185. Weil, M. H.: Disseminated lupus erythematosus with massive hemorrhagic manifestations and paraplegia, Journal Lancet 75: 358 (Aug.) 1955.
- 2186. Weinberger, H. J., and Bauer, W.: Diagnosis and treatment of Reiter's syndrome, M. Clin. North America 39: 587 (Mar.) 1955.
- 2187. Weiner, M., Chenkin, T., and Burns, J. J.: Observations on the metabolic transformation and effects of phenylbutazone in subjects with hepatic disease, Am. J. M. Sc. 228: 36 (July) 1954.
- 2188. Weinstein, A. B., and Kurtz, C. M.: Long-term Aureomycin administration in the prevention of rheumatic fever, Wisconsin M. J. 54: 423 (Sept.) 1955.
- 2189. Weinstein, L., Fraerman, S. H., and Lewin, P.: Difficulties in early diagnosis of myositis ossificans, J. A. M. A. 154: 994 (Mar. 20) 1954.
- 2190. Weinstein, L., Boyer, N. H., and Goldfield, M.: Rheumatic heart disease in scarlet-fever patients treated with penicillin, New England J. Med. 253: 1 (July 7) 1955.

- 2191. Weisman, J. I., and Bloom, B.: Anuria following phenylbutazone therapy, New England J. Med. 252: 1086 (June 23) 1955.
- 2192. Weiss, E.: Psychogenic rheumatism, M. Clin. North America 39: 601 (Mar.) 1955.
- 2193. Weiss, L.: A metastasizing ependymoma of the cauda equina, Cancer 8: 161 (Jan.) 1955.
- 2194. Weiss, R. S., and Swift, S.: The significance of a positive L. E. phenomenon, Arch. Dermat. and Syph. 72: 103 (Aug.) 1955.
- 2195. Weiss, T. E., Duncan, T., and de la Cruz, B.: The local injection of hydrocortisone in the treatment of the painful joint, J. M. A. Georgia 43: 629 (July) 1954.
- 2196. Weiss, T. E.: Rheumatism resembling rheumatoid arthritis, J. Louisiana M. Soc. 107: 147 (Apr.) 1955.
- 2197. Weissmann, B., Bromberg, P. A., and Gutman, A. B.: Chromatographic investigation of purines in normal human urine, Proc. Soc. Exper. Biol. and Med. 87: 257 (Oct.) 1954.
- 2198. West, H. F.: Ankylosing spondylitis, Medicine Illus. (London) 9: 521 (Aug.) 1955.
- 2199. West, H. F., and Newns, G. R.: Ankylosing spondylitis and prolonged ACTH therapy, Ann. Rheumat. Dis. 13: 109 (June) 1954.
- 2200. West, H. F., and Newns, G. R.: Cortisone and rheumatoid disease, Lancet 2: 1123 (Nov. 28) 1953.
- 2201. West, H. F., and Newns, G. R.: Cortisone acetate v. cortisol in the treatment of rheumatoid disease, Lancet 2: 168 (July 24) 1954.
- 2202. West, H. F.: Effects of 9-alpha fluoro hydrocortisone acetate on adrenal function, Ann. Rheumat. Dis. 14: 170 (June) 1955.
- 2203. West, H. F.: Purified ACTH gel control of therapy in rheumatoid patients, Ann. Rheumat. Dis. 13: 56 (Mar.) 1954.
- 2204. West, H. F.: Some observations on the urinary excretion of 17-ketosteroids and 17-ketogenic steroids in patients receiving ACTH, J. Endocrinol. 10: 12, 1954.
- 2205. West, H. F., and Newns, G. R.: Treatment of rheumatoid arthritis by prolonged stimulation of the adrenal cortex, Lancet 1: 578 (Mar. 19) 1955.
- 2206. Westergren, A.: On serum titres, multiple infections, and complex aetiology in chronic polyarthritis, Acta med. Scandinav. 147: 387, 1954.
- 2207. "What is the prevalence and cost of arthritis and rheumatism?" "What is being done for people with these diseases?", National Health Education Committee, New York, 1956.
- 2208. "What is the prevalence and cost of arthritis and rheumatism?" "What is being done for people with these diseases?," National Health Education Committee, New York. 1957.
- 2209. Wheatley, G. M., and Lewy, F. J.: Community rheumatic fever programs, Pediatrics 14: 78 (July) 1954.
- 2210. White, J. W.: Conservative nonoperative treatment of lumbar disk lesions, Postgrad. Med. 16: 488 (Dec.) 1954.
- 2211. Whitelaw, G. P.: The therapeutic use of procaine hydrochloride injection, M. Clin. North America 39: 1503 (Sept.) 1955.
- 2212. Wickman, W., and Lamphier, T. A.: DeQuervain's disease, a survey of forty-seven cases, J. Florida M. A. 41: 36 (July) 1954.
- 2213. Wickstrom, J., Haslam, E. T., and Hutchinson, R. H.: Backache during pregnancy; its etiology and management, J. Louisiana M. Soc. 107: 490 (Dec.) 1955.
- 2214. Wierman, W. H., Clagett, O. T., and McDonald, J. R.: Articular manifestations in pulmonary diseases: an analysis of their occurrence in 1,024 cases in which pulmonary resection was performed, J. A. M. A. 155: 1459 (Aug. 21) 1954.
- 2215. Wiesel, L. L., and Barritt, A. S.: Long term treatment of rheumatoid arthritis with para-aminobenzoic acid and cortisone acetate, Am. J. M. Sc. 227: 74 (Jan.) 1954.
- 2216. Wilcox, E. B., and Galloway, L. S.: Children with and without rheumatic fever.
 I. Nutrient intake, physique, and growth, J. Am. Dietet. A. 30: 345 (Apr.) 1954.

2217. Wilcox, E. B., and Galloway, L. S.: Children with and without rheumatic fever. II. Food habits, J. Am. Dietet. A. 30: 453 (May) 1954.

2218. Wilcox, E. B., Galloway, L. S., Wood, P., and Mangelson, F. L.: Children with and without rheumatic fever. III. Blood serum vitamins and phosphatase data, J. Am.

Dietet. A. 30: 1231 (Dec.) 1954.

2219. Wilcox, E. B., Mangelson, F. L., Galloway, L. S., and Wood, P.: Children with and without rheumatic fever. IV. Hemoglobin, packed red cells, red and white cell count, sedimentation rate, blood glucose, serum iron and copper, J. Am. Dietet. A. 31: 45 (Jan.) 1955.

2220. Wilhelmj, C. M., Shuput, D., Gunderson, D. E., and McCarthy, H. H.: Relative sensitivity of circulating eosinophils and capillary resistance to exogenous cortisone,

Proc. Soc. Exper. Biol. and Med. 89: 119 (May) 1955.

- 2221. Wilhelmj, C. M., Gunderson, D. E., Shuput, D., and McCarthy, H. H.: A study of certain antagonistic actions of pituitary growth hormone and cortisone, J. Lab. and Clin. Med. 45: 516 (Apr.) 1955.
- 2222. Wilkinson, M. C.: Chemotherapy of tuberculosis of bones and joints, J. Bone and Joint Surg. 36B: 23 (Feb.) 1954.

2223. Wilkinson, M. C.: Developments in the treatment of bone and joint tuberculosis, Brit. M. Bull. 10: 130, 1954.

- 2224. Wilkinson, M. C.: The treatment of tuberculosis of the spine by evaluation of the paravertebral abscess and curettage of the vertebral bodies, J. Bone and Joint Surg. 37B: 382 (Aug.) 1955.
- 2225. Williams, A. W.: Influence of cortisone on the healing of gastric ulcers, J. Path. and Bact. 67: 259 (Jan.) 1954.
- 2226. Williams, E. R.: Observations on the differential diagnosis and sequelae of juvenile vertebral osteochondrosis, Acta radiol. Supp. 116: 293, 1954.
- 2227. Williams, G.: A histological study of the connective tissue reaction to carrageenin, J. Path. and Bact. 73: 557 (Apr.) 1957.
- 2228. Williams, P. C.: Examination and conservative treatment for disk lesions of the lower spine, Clin. Orthop. 5: 28, 1955.
- 2229. Williams, R.: Complete protrusion of a calcified nucleus pulposus in the thoracic spine, J. Bone and Joint Surg. 36B: 597 (Nov.) 1954.
- 2230. Williams, R. G.: The effects of continuous local injection of hyaluronidase on skin and subcutaneous tissue in rats, Anat. Rec. 122: 349 (July) 1955.

2231. Willis, T. A.: The inadequate back, Clin. Orthop. 5: 17, 1955.

- 2232. Wilson, D., Beyer, A., Bishop, C., and Talbott, J. H.: Urinary uric acid excretion after the ingestion of isotopic yeast nucleic acid in the normal and gouty human, J. Biol. Chem. 209: 227 (July) 1954.
- 2233. Wilson, H., Fairbanks, R., McEwen, C., and Ziff, M.: Studies on the metabolism of adrenal cortical steroids in the synovial cavity in rheumatoid arthritis, Ann. New York Acad. Sc. 61: 502 (May 27) 1955.
- 2234. Wilson, J. C., Jr.: Childhood limp, diagnosis and treatment, Pediat. Clin. North America 2: 1021 (Nov.) 1955.
- 2235. Wilson, J. F.: A serological study of Neisseria gonorrhoeae, J. Path. and Bact. 68: 495 (Oct.) 1954.
- 2236. Wilson, J. N.: Profiles of the carpal canal, J. Bone and Joint Surg. 36A: 127 (Jan.) 1954.
- 2237. Wilson, M. G., and Schweitzer, M.: Pattern of hereditary susceptibility in rheumatic fever, Circulation 10: 699 (Nov.) 1954.
- 2238. Wilson, R. A., Danto, J. L., and Maddin, S.: Electron microscopy of collagen fibrils during cortisone therapy of alopecia totalis (technical problems), J. Invest. Dermat. 25: 175 (Sept.) 1955.
- 2239. Wilson, R. N., and Wilson, S.: Low backache in industry, a review of 1,163 cases, Brit. M. J. 2: 649 (Sept. 10) 1955.

- 2240. Wilson, T. G.: Dermatomyositis, Arch. Middlesex Hosp. 4: 151 (July) 1954.
- 2241. Wirtschafter, Z. T., Williams, D. W., and Gaulden, E. C.: Palindromic rheumatism, a clinical description and an electrophoretic analysis of the synovial fluid, Acta med. Scandinav. 153: 119, 1955.
- 2242. Wise, C. S., and Ardizzone, J.: Electromyography in intervertebral disc protrusions, Arch. Phys. Med. 35: 442 (July) 1954.
- 2243. Wolfson, W. Q.: Polycyclic continuous acute gouty arthritis, J. Michigan M. Soc. 54: 323 (Mar.) 1955.
- 2244. Wolfson, W. Q.: Present status of ACTH, hydrocortisone, and cortisone with particular references to long-term treatment, Mississippi Valley M. J. 77: 66 (Mar.) 1955.
- 2245. Wolfson, W. Q.: The prevention of adrenal atrophy during prolonged treatment with large doses of oral hydrocortisone, J. Lab. and Clin. Med. 44: 956 (Dec.) 1954.
- 2246. Wolkin, J., Sachs, M. D., and Hoke, G. H.: Comparative studies of discography and myelography, Radiology 64: 704 (May) 1955.
- 2247. Wollaeger, E. E.: Untoward effects of cortisone and corticotropin on the gastrointestinal tract, Minnesota Med. 37: 626 (Sept.) 1954.
- 2248. Wood, G. C.: Some tensile properties of elastic tissue, Biochim. et Biophys. Acta 15: 311 (Nov.) 1954.
- 2249. Wood, H. F., and McCarty, M.: Laboratory aids in the diagnosis of rheumatic fever and in evaluation of disease activity, Am. J. Med. 17: 768 (Dec.) 1954.
- 2250. Wood, H. F., McCarty, M., and Slater, R. J.: The occurrence during acute infections of a protein not normally present in the blood. V. Physical-chemical properties of the C-reactive protein crystallized by a modified technique, J. Exper. Med. 100: 71 (July) 1954.
- 2251. Wood, I. H.: Fatal case of agranulocytosis following phenylbutazone, Brit. M. J. 1: 802 (Apr. 3) 1954.
- 2252. Woodmansey, A., and Beattie, J. W.: Effect of cortisone and certain other steroids on the peripheral vasculature in arthritis, Ann. Rheumat. Dis. 14: 293 (Sept.) 1955.
- 2253. Woods, W. W., and Shea, P. A.: The anterior scalene syndrome, a reevaluation of signs, symptoms and treatment, West. J. Surg. 63: 682 (Nov.) 1955.
- 2254. Woolnough, J.: Tennis heel, M. J. Australia 2: 857 (Nov. 27) 1954.
- 2255. Woolsey, R. D.: The mechanism of neurological symptoms and signs in spondylolisthesis at the fifth lumbar, first sacral level, South. M. J. 47: 643 (July) 1954.
- 2256. World Health Organization: Expert committee on rheumatic diseases, first report, 1954, Ann. Rheumat. Dis. 13: 253 (Sept.) 1954.
- 2257. Wornom, P. H., and Swineford, O., Jr.: Phenylbutazone (Butazolidin) in the treatment of various rheumatic disorders, Virginia M. Monthly 82: 176 (Apr.) 1955.
- 2258. Worthington, C. R., and Tomlin, S. G.: Small-angle x-ray diffraction patterns of collagen, Nature, London 175: 811 (May 7) 1955.
- 2259. Wyngaarden, J. B.: The effect of phenylbutazone on uric acid metabolism in two normal subjects, J. Clin. Investigation 34: 256 (Feb.) 1955.
- 2260. Wyngaarden, J. B., Peterson, R. E., and Wolff, A. R.: Physiologic disposition of radiometabolites of hydrocortisone-4-C¹⁴ in the rat and guinea pig, J. Biol. Chem. 212: 963 (Feb.) 1955.
- 2261. Wyngaarden, J. B.: Uric acid, in Cyclopedia of Medicine, Surgery and Specialties, 1955, F. A. Davis Company, Philadelphia, p. 341.
- 2262. Wynn-Williams, N., and Edwards, G. F.: Bilateral hilar lymphadenopathy, its association with erythema nodosum, Lancet 1: 278 (Feb. 6) 1954.
- 2263. Yaffee, H. S.: A peculiar nodosity associated with arthritis, U. S. Armed Forces M. J. 6: 1043 (July) 1955.

- 2264. Yaskin, J. C., Rupp, C., Hirschfield, B. A., and Groff, R. A.: Experience with cervical intervertebral disc protrusions, a report of 66 surgically verified cases, Tr. Am. Neurol. A. 79: 89, 1954.
- 2265. Yedinak, P. R., and Holbrook, B. G.: Bicipital tenosynovitis, Rocky Mountain M. J. 51: 185 (Mar.) 1954.
- 2266. Yegge, W. B.: Intermittent hydrarthrosis, Rocky Mountain M. J. 52: 438 (May) 1955.
- 2267. Yeoman, W.: The place of physiotherapy in the treatment of the rheumatic disorders, Brit. J. Phys. Med. 18: 76 (Apr.) 1955.
- 2268. Yielding, K. L., Platt, D., and Holley, H. L.: Synovial fluid. I. Comparison of sodium and potassium concentrations in normal and diseased joint fluid, Proc. Soc. Exper. Biol. and Med. 85: 665 (Apr.) 1954.
- 2269. Yost, J., Winters, T., and Fetts, H. C., Sr.: Dupuytren's contracture, a statistical study, Am. J. Surg. 90: 568 (Oct.) 1955.
- 2270. Young, H. H.: Lesions of the hip joint: primary acetabular pathologic changes and primary synovial changes, Proc. Staff Meet., Mayo Clin. 29: 41 (Jan. 27) 1954.
- 2271. Young, H. H., Love, J. G., Svien, H. J., Price, R. D., and Kroll, H. G.: Low back and sciatic pain: long-term results after removal of protruded intervertebral disk with or without fusion, Clin. Orthop. 5: 128, 1955.
- 2272. Young, H. H., Ward, L. E., and Henderson, E. D.: The use of hydrocortisone acetate (compound F acetate) in the treatment of some common orthopaedic conditions, J. Bone and Joint Surg. 36A: 602 (June) 1954.
- 2273. Young, J. M., and Hudacek, A. G.: Experimental production of pigmented villonodular synovitis in dogs, Am. J. Path. 30: 799 (July) 1954.
- 2274. Yü, T. F., Sirota, J. H., and Gutman, A. B.: Effect of phenylbutazone (3,5 dioxo-1,2-diphenyl-4-n-butylpyrazolidine) on a renal clearance of urate and other discrete renal functions in gouty subjects, J. Clin. Investigation 32: 1121 (Nov.) 1953.
- 2275. Yü, T. F., and Gutman, A. B.: Paradoxical retention of uric acid by uricosuric drugs in low dosage, Proc. Soc. Exper. Biol. and Med. 90: 542 (Nov.) 1955.
- 2276. Yü, T. F., and Gutman, A. B.: Quantitative analysis of uric acid in blood and urine; methods and interpretation, Bull. Rheumat. Dis. 7: (Supp.) S 17 (Jan.) 1957.
- 2277. Yü, T. F., Wasserman, L. R., Benedict, J. D., Bien, E. J., Gutman, A. B., and Stetten, D., Jr.: A simultaneous study of glycine-N¹⁸ incorporation into uric acid and heme, and of Fe¹⁰ utilization, in a case of gout associated with polycythemia secondary to congenital heart disease, Am. J. Med. 15: 845 (Dec.) 1953.
- 2278. Yuhl, E. T., Hanna, D., Rasmussen, T., and Richter, R. B.: Diagnosis and surgical therapy of chronic midline cervical disk protrusions, Neurology 5: 494 (July) 1955.
- 2279. Yules, J. H.: Ochronotic arthritis, Bull. New England M. Center 16: 168 (Dec.) 1954.
- 2280. Zacco, M., Richardson, E. M., Crittenden, J. O., Hollander, J. L., and Dohan, F. C.: Disposition of intra-articularly injected hydrocortisone acetate, hydrocortisone and cortisone acetate in arthritis. I. Concentrations in synovial fluid and cells, J. Clin. Endocrinol. 14: 711 (July) 1954.
- 2281. Zacco, M., Richardson, E. M., Crittenden, J. O., Dohan, F. C., and Hollander, J. L.: Disposition of intra-articularly injected hydrocortisone acetate, hydrocortisone free alcohol and cortisone acetate in arthritis, Experientia 11: 279 (July) 1955.
- 2282. Zachariae, L., and Zachariae, F.: Hydrocortisone acetate in the treatment of Dupuytren's contracture and allied conditions, Acta chir. Scandinav. 109: 421, 1955.
- 2283. Zachariae, L., and Moltke, E.: Influence of hydrocortisone (compound F) on mast cells of normal skin and healing wounds in the rabbit, Acta endocrinol. 16: 300, 1955.
- 2284. Zachariae, L.: Hydrocortisone acetate applied intraperitoneally. I. Inhibitory effect on adhesions produced by talc, Acta endocrinol. 16: 149, 1954.

- 2285. Zachariae, L.: Hydrocortisone acetate applied intraperitoneally. II. Inhibitory effect on adhesions produced by serosal injury. III. Inhibitory effect on reformation of surgically separated adhesions, Acta endocrinol. 19: 269, 1955.
- 2286. Zarrow, M. X., Holmstrom, E. G., and Salhanick, H. A.: The concentration of relaxin in the blood serum and other tissues of women during pregnancy, J. Clin. Endocrinol. 15: 22 (Jan.) 1955.
- 2287. Zeman, F. D.: Genetic factors in the diseases of later life, J. Chron. Dis. 2: 11 (July) 1955.
- 2288. Zevely, H. A., French, A. J., Mikkelsen, W. M., and Duff, I. F.: Synovial specimens obtained by knee joint punch biopsy, Am. J. Med. 20: 510 (Apr.) 1956.
- 2289. Ziff, M.: The agglutination reaction in rheumatoid arthritis, J. Chron. Dis. 5: 644 (June) 1957.
- 2290. Ziff, M., Simson, J., Scull, E., Smith, A., Shatton, J., and Mainland, D.: Amino-tripeptidase content of synovial fluid in arthritic diseases, J. Clin. Investigation 34: 27 (Jan.) 1955.
- 2291. Ziff, M., Brown, P., Badin, J., and McEwen, C.: A hemagglutination test for rheumatoid arthritis with enhanced sensitivity using the euglobulin fraction, Bull. Rheumat. Dis. 5: 75 (Oct.) 1954.
- 2292. Zimmer, F. E.: Difficulties encountered in the therapeutic use of cortisone and ACTH, Am. Pract. and Digest Treat. 5: 511 (July) 1954.
- 2293. Zimmerman, H. J., Kleitsch, W. P., Greene, A. M., and McFadden, H. F., Jr.: Periarteritis (polyarteritis) nodosa producing intussusception, Arch. Int. Med. 94: 264 (Aug.) 1954.
- 2294. Zion, M. M., Goldberg, B., and Suzman, M. M.: Corticotrophin and cortisone in the treatment of scleroderma, Quart. J. Med. 24: 215 (July) 1955.
- 2295. Zivin, S., Steck, I. E., Montgomery, M. M., Kaiser, G. D., and Bennett, G. A.: An evaluation of the effects of cortisone on the subcutaneous nodules of patients with rheumatoid arthritis, J. Lab. and Clin. Med. 43: 70 (Jan.) 1954.
- 2296. Zondek, S. G.: Inhibiting influence of essential hypertension on malignant growth and rheumatoid arthritis, Acta med. Scandinav. 152: 231, 1955.
- 2297. Zuckner, J.: Rheumatoid arthritis in the aged, Missouri Med. 52: 788 (Oct.) 1955.
- 2298. Zuckner, J.: Vitamin B₁₂ therapy in osteoarthritis, Missouri Med. 51: 450 (June)
- 2299. Zumoff, B.: Failure of folic acid to affect uric acid metabolism in a case of gout, Metabolism 4: 80 (Jan.) 1955.

RECENT BOOKS

- Asboe-Hansen, G., Editor: Connective tissue in health and disease, 1954, Munksgaard, Copenhagen, Denmark.
- Block, W., and Van Goor, K.: Metabolism, pharmacology and therapeutic uses of gold compounds, 1956, Charles C Thomas, Springfield, Ill.
- Brugsch, Heinrich G.: Rheumatic diseases, rheumatism and arthritis, 1957, J. B. Lippincott Company, Philadelphia.
- 4. Bunim, J. J., Editor: Research and education in rheumatic diseases, Transactions of First National Conference at National Institutes of Health, 1954, Arthritis and Rheumatism Foundation, New York, in coöperation with National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md.
- Bunim, J. J., Editor: Research and education in rheumatic diseases, Transactions of Second National Conference at National Institutes of Health, 1957, Arthritis and Rheumatism Foundation, New York, in cooperation with National Institute of Arthritis and Metabolic Diseases, Public Health Service, Bethesda, Md.
- 6. Buxton, St. J. D.: Arthroplasty, 1955, J. B. Lippincott Company, Philadelphia.

- Ciba Foundation, Editors: Symposium on the chemistry and biology of mucopolysaccharides, 1958, Little, Brown and Company, Boston, Mass.
- Copeman, W. S. C.: Textbook of the rheumatic diseases, 2nd Ed., 1955, E. & S. Livingstone, Ltd., Edinburgh and London.
- 9. Goff, C. W.: Legg-Calve-Perthes syndrome, 1954, Charles C Thomas, Springfield, Ill.
- Goslings, J., and Van Swaay, H.: Contemporary rheumatology, Proceedings of the Third European Rheumatology Congress, 1956, Elsevier Publishing Company, New York.
- Jakobsen, A.: Vitallium mould arthroplasty for osteoarthritis of the hip joint, 1957, The Macmillan Company, New York.
- Judet, J., Judet, R., Lagrange, J., and Dunoyer, J.: Resection-reconstruction of the hip, 1954, E. & S. Livingstone, Ltd., Edinburgh and London.
- Lamont-Havers, R. W., Editor: Serological reactions of rheumatoid arthritis, Summary of First Conference, 1958, Arthritis and Rheumatism Foundation, New York.
- McKusick, V. A.: Heritable disorders of connective tissue, 1956, The C. V. Mosby Company, St. Louis.
- Palumbo, L. T.: Low back pain and sciatica, 1954, J. B. Lippincott Company, Philadelphia.
- Ragan, Charles, Editor: Connective tissues, Transactions of the Fifth Conference, 1954, Josiah Macy, Jr. Foundation, New York.
- 17. Romanus, R., and Ydén, S.: Pelvo-spondylitis ossificans, 1955, Munksgaard, Copenhagen, Denmark.
- Ropes, M. W., and Bauer, W.: Synovial fluid changes in joint disease, 1953, published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass.
- Short, C. L., Bauer, W., and Reynolds, W. E.: Rheumatoid arthritis, 1957, published for the Commonwealth Fund by Harvard University Press, Cambridge, Mass.
- Steinberg, C. L., with five contributors: Arthritis and rheumatism, 1954, Springer Publishing Company, Inc., New York.
- Symposium organized by the Council for International Organizations of Medical Sciences: Connective tissue, 1957, Charles C Thomas, Springfield, Ill.
- 22. Talbott, J.: Gout, 2nd Ed., 1957, Grune & Stratton, New York.
- Talbott, J. H., and Ferrandis, R. M.: Collagen diseases, 1956, Grune & Stratton, New York.
- Talbott, J. H., and Lockie, L. M.: Progress in arthritis, 1958, Grune & Stratton, New York.

CASE REPORTS

SERUM HYPERTONICITY SECONDARY TO CEREBRAL DISEASE *

By Marvin F. Levitt, M.D., Marvin Belsky, M.D., New York, N. Y., and Demetra Polimeros, B.S., Brooklyn, N. Y.

The development of serum hypertonicity in patients with primary cerebral disease is well known, 1-18 although many of the reported cases do not fulfill the criteria which characterize this form of serum hypertonicity. The cerebral disease and its manifestations must precede the progressive elevation of the serum electrolyte concentrations. This sequence excludes the possibility that the hypertonicity and cerebral dysfunction stem from inadequate water intake with severe dehydration. Water intake should reach levels generally considered to be adequate, and the mean electrolyte concentration of the total intake should not exceed the tonicity of normal plasma. Finally, renal function should be reasonably well preserved, so that the hypertonicity may not be attributed to the marked water wastage of profound renal failure.

Recently we encountered a patient who, one month after operation for a recurrent occipital meningioma, developed meningitis and thereafter serum hypertonicity. Of particular interest was the reversal of this syndrome with the subsidence of the meningitis, as almost all previous cases have either died or remained with persistently elevated concentrations of serum sodium and chloride. It was possible to perform balance studies during that period of the syndrome when the serum electrolytes were returning to normal. By means of defining the alterations which occurred during the recovery phase, some insight has been acquired into the mechanisms which produce serum hypertonicity during the course of cerebral disease.

CASE REPORT

A 38 year old housewife entered The Mount Sinai Hospital on September 26, 1956, with recurrence of a left occipital meningioma. The patient had had a partial excision of a large meningioma in the left occipital area on September 6, 1955, after a two-year history of left supra-orbital headache, bilateral papilledema and a right homonymous hemianopsia. Following the operation, weakness of the right upper extremity developed. One year later, because of rapidly progressive right-sided motor weakness, bulging decompression flaps, persistent chronic papilledema and right homonymous hemianopsia, the patient was rehospitalized.

Following the sudden onset of semistupor and fever of one day's duration, a left occipital craniotomy was performed on October 23, 1956, with the partial removal

* Received for publication April 8, 1958.

From the Departments of Medicine and Pediatrics, The Mount Sinai Hospital, New York N. V.

Requests for reprints should be addressed to Marvin F. Levitt, M.D., The Mount Sinai Hospital, New York 29, N. Y.

ARIF

| | 7 | *** | | Urine | Urine Concentrations | ations | | Total | Total Urine Excretion | retion | | | Serum Concentrations | centration | 80 | |
|------|-----------------------------|-----------------------------|---------|-----------------------------------|-------------------------|---------------------------|---------------------------------|-----------------------------|-------------------------------|-------------------------------------|-----------------------------------|-------------------------|---------------------------|---------------------------------|------------------|--------------------------|
| Date | Intake (c.c./ 24 hr.) | Output (c.c./ 24 hr.) | Sp. Gr. | Osmola- rity (mOsm./ L.) | Sodium (mEq./ L.) | Chloride (mEq./ L.) | Potas- sium (mEq./ L.) | Sodium (mEq./ 24 hr.) | Chloride (mEq./ 24 hr.) | Potas- sium (mEq./ 24 hr.) | Osmola- rity (mOsm./ L.) | Sodium (mEq./ L.) | Chloride (mEq./ L.) | Potas- sium (mEq./ L.) | B.U.N. (mg.%) | Bicarb. (mEq./ L.) |
| /27 | 1,020 | 800 | | | | | | | - | | | | | | | |
| /29 | 1,200 | 450 | | | _ | | | | | | | 140 | 66 | 3.6 | 00 | 1 |
| 130 | 2,200 | 1,300 | | | | | | | | | | 152 | 112 | 5.3 | 10 | 11.5 |
| 375 | 2,300 | 1,500 | 1.016 | | | | | | | | | 169 | 124 | 3.1 | 17 | 35 |
| 14 | 2,500 | 1,500 | 2 | | | | | | | | | 107 | 14.1 | | | 2000 |
| 100 | 2,200 | 1,500 | 1.016 | | | | | | | | | 178 | 133 | 3.7 | 18 | 29.2 |
| 12/7 | 2,400 | 1,700 | 1.029 | 928 | 225 | 189 | 57.5 | 383 | 321 | 98 | 326 | 30 | 124 | | | |
| 6/ | 3,000 | 009 | 1.031 | 933 | 207 | 154 | 74.0 | 125 | 93 | 4 | 296 | 150 | 105 | 6.5 | 14 | |
| 110 | 2,400 | 009 | 1.029 | 955 | 158 | 129 | 70.0 | 94 | 78 | 42 | 287 | 145 | 104 | 4.3 | | |
| /11 | 2,600 | 200 | 1.029 | 970 | 120 | 86 | 81.0 | 09 | 49 | 41 | 277 | 138 | 102 | 5.0 | | |
| /13 | 1,890 | 400 | 1.028 | 918 | 38 | 77 | 53.0 | 15 | 31 | 21 | 276 | 135 | 66 | | | |
| /14 | 1,500 | 710 | 1.019 | 471 | 21 | 47 | 48.0 | 15 | 33 | 34 | 264 | 135 | 97 | 4.2 | | |
| /15 | 15,00 | 820 | 1.018 | 413 | 16 | 45 | 44.0 | 12 | 34 | 34 | 266 | 132 | 97 | | 12 | |

of a recurrent meningioma. During the next few weeks the patient had some leakage of cerebrospinal fluid at the site of the wound, for which therapeutic lumbar taps were performed frequently, with some degree of success. Her sensorium was quite clear after the operation, and she was able to sit up and talk with relatives. Her food and fluid intake and urinary output were adequate.

On November 25, a month after her operation, the patient became confused and febrile. Spinal tap revealed a turbid fluid containing 335 white blood cells per cubic centimeter, of which 94% were neutrophils. An enterococcus was cultured from this fluid, and the patient was started on intensive combined therapy with erythromycin and Chloromycetin. During the ensuing 10-day period it was noted that the serum sodium and chloride concentrations progressively rose from normal values on Novem-

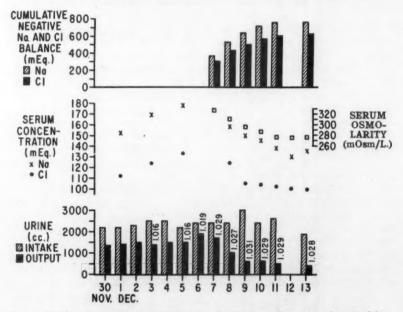


Fig. 1. Fluid and electrolyte data during and after recovery from serum hypertonicity.

ber 30 to peak concentrations of 178 and 133 mEq./L. for sodium and chloride, respectively, on December 5 (figure 1, table 1). Throughout this period the patient received a total fluid intake of between 2,000 and 2,500 c.c. daily, parenterally, orally or by tube. No serious attempt was made to limit the salt intake, and approximately one third of the parenteral infusions was isotonic saline. Similarly, the diet and tube feedings contained normal quantities of salt. No hypertonic salt infusions were administered at any time during her course. The blood urea ranged between 10 and 18 mg.%, but the specific gravity of the urine specimens was recorded as 1.016 in the face of a rapidly rising serum tonicity (table 1). At no time did the patient show any signs of dehydration, nor did the hemoglobin concentrations reflect any evidence of hemoconcentration. Because of the rising serum electrolyte concentration, the patient was switched to salt-free tube feedings on the evening of December 5.

During the period of rising plasma osmolarity there were occasional spikes of

fever as high as 104° F. On December 5, several days after she had "appeared terminal," some clinical improvement and considerable clearing in her sensorium were noted. At this point her serum electrolytes were at their peak concentrations, yet her spinal fluid seemed clearer and contained fewer white cells. On December 9 the patient seemed "more intelligible," and the temperature fell to normal. The following day the spinal fluid contained only 32 white cells, most of which were lymphocytes. The serum electrolyte concentration reached normal by December 12.

The patient's chief problem thereafter was continued spinal fluid drainage from the scalp wound, which would periodically break down. She exhibited increasing strength of her right side, and she was able to sit up out of bed and raise her right arm above her head.

Methods and Results: Metabolic studies were initiated on the evening of December 6, 1956, at which point the plasma sodium and chloride concentrations were close to their peak concentrations (table 1). At this time she was on a daily intake by means of a gastric tube of 2,400 c.c. of a protein and carbohydrate mixture. This quantity of feeding contained 15 mEq. of sodium chloride and 35 mEq. of potassium. The precise fluid and salt intake is therefore known from December 6 through December 15, 1956. During this interval all the urine was collected and its daily volume, electrolyte composition and osmolarity were measured. Similar daily measurements of serum were made. The methods of analyses are similar to those previously reported from this laboratory. The prior to December 6 the measurements were performed by hospital routine laboratories.

From December 6 through 11 the serum osmolarity fell 45 milliosmols/Kg. H₂O, and the serum sodium and chloride concentrations each fell 30 mEq./L. (figure 1, table 1). A total of 835 and 677 mEq. of sodium and chloride, respectively, were excreted, while the total salt intake was 75 mEq., establishing a negative balance of sodium and chloride of 760 and 600 mEq., respectively (figure 1, table 1). Urine concentration rose to almost 1,000 milliosmols/Kg. H₂O, or a specific gravity close to 1.030. The elaboration of a maximally concentrated urine occurred despite a considerable fluid intake (figure 1, table 1). After the plasma electrolyte concentrations fell to normal, urine concentrations fell to 500 milliosmols/Kg. H₂O, and salt excretion decreased to levels commensurate with the intake.

Discussion

The loss of 600 and 750 mEq. of chloride and sodium, respectively, during the recovery phase argues that a considerable reduction in total extracellular volume as well as in its tonicity occurred during this period. A comparable salt diuresis, without a change in extracellular volume, and coexistent with a fall in serum salt concentration of approximately 30 mEq. per liter, would demand an extracellular volume of approximately 20 to 25 L. Such a volume would exceed by more than two times the normal extracellular volume of a patient this size.18 However, neither edema nor other clinical manifestations of a markedly expanded extracellular volume existed prior to the diuresis. Furthermore, this large loss of salt excludes the likelihood that any reduction in extracellular volume or significant degree of dehydration existed prior to the diuresis. If a depleted extracellular volume had lost so much salt, the remaining fluid stores would not be compatible with life, let alone a moderately good state of hydration. Accordingly, it seems most likely that prior to the diuresis there existed in this patient a moderately expanded extracellular volume of higher electrolyte concentration than normal. The marked salt diuresis was not associated with a comparable loss of water. The elaboration of markedly concentrated urine in

the face of an adequate water intake suggested that water was being retained. This implies that a considerable transfer of water into cells occurred in association with the negative salt balance.

If we assume that the events which transpired during the development of this syndrome represent the opposite of those observed during the subsequent recovery period, it seems likely that the development of primary cerebral hypertonicity is characterized by (1) an inability to elaborate a urine of appropriate osmolarity, causing a relatively inadequate conservation of water and a rising serum tonicity, (2) marked sodium and chloride retention, with expansion of the extracellular volume, and (3) a shift of water from cells outward secondary to the rising extracellular fluid osmolarity.

Several observations made in this patient and others reported from similar cases appear to justify the above assumption. While serum hypertonicity was rising, the specific gravity of the urine ranged between 1.014 and 1.016 (figure 1, table 1). There was no evidence of renal failure during this period or thereafter to account for this inability to produce an appropriately concentrated urine. The ability to produce a urine of maximal osmolarity during the recovery phase indicated that no renal failure had preëxisted. Previous reports have emphasized the presence of a markedly reduced rate of sodium and chloride excretion despite the rising plasma salt concentrations. 1. 3, 6, 8

Any hypothesis suggested to explain the mechanism whereby this syndrome develops must offer a reasonable explanation for the phenomena which produce serum hypertonicity in cerebral disease. Peters originally explained the serum hypertonicity as the inability to elaborate an antidiuretic hormone, with consequent water loss, dehydration and hypertonicity, as in classic diabetes insipidus.4 Although such a hypothesis cannot be completely ruled out, there are certain lines of evidence which render this conclusion unlikely. Peters himself later noted that the serum hypertonicity associated with intracranial disorders did not respond promptly to large quantities of salt-free fluid, as did the hypertonicity in patients with the usual dehydration of diabetes insipidus. 19, 20 He also pointed out that patients with diabetes insipidus tend to be in a continuous state of mild dehydration with a reduced extracellular volume.20 This finding is not in accord with the enlarged extracellular volume observed in this patient. The conspicuous polyuria which is characteristic of the patient with diabetes insipidus, particularly if a high solute load is exhibited,21 22 was not present in this patient or in others described. When the patient with diabetes insipidus develops a serum hypertonicity of this degree he is so dehydrated that he may be critically sick and on the verge of shock. Such was not the case in the patient studied here or in many others reported with this syndrome. These lines of reasoning tend to weaken the hypothesis that primary cerebral hypertonicity simply represents the inability to elaborate antidiuretic hormone, as in typical diabetes insipidus. Recently a form of nephrogenic diabetes insipidus has been studied in which the renal parenchyma is unresponsive to antidiuretic hormone.28 However, the capacity to produce a maximally concentrated urine during the recovery phase is difficult to associate with tubules that are nonresponsive to antidiuretic hormone.

A sharp transient increase in serum electrolyte concentrations has been shown to occur in experimental animals and man following electroshock therapy.²⁴ In addition, several cases of more prolonged serum hypertonicity have been reported after electroshock treatment.²⁸ On the basis of these observations some have argued that the serum hypertonicity of cerebral disease represents the effects of a primary increase in osmotically active intracellular base. In this view, intracerebral disease could precipitate basic alterations in cellular physiology characterized by a marked increase in cellular tonicity.^{26–28} This phenomenon would then initiate a transfer of water into the cells, and finally an increase in extracellular osmolarity. A primary increase in cellular tonicity, however, would not explain the inability to elaborate a urine of maximal concentration. This alternative hypothesis, then, does not seem to explain all the phenomena which distinguish primary cerebral hypertonicity.

The most plausible hypothesis would place the defect in the afferent portion of the cerebral osmoreceptor mechanism.^{20, 80} In this view, the cerebral disease triggers a decrease in the sensitivity of the "osmostat," so that progressively higher osmolarities are required to initiate a response. As the sensitivity of this afferent limb progressively falls, the response to increasing hyperosmolarity becomes increasingly inadequate and the formation of antidiuretic hormone woefully insufficient.

This form of insufficiency of antidiuretic hormone is cumulative and incomplete, and is thereby distinguished from the frank failure of antidiuretic hormone formation typical of classic diabetes insipidus. In this syndrome, concentration of the urine to osmolarities of 400 to 500 milliosmols/Kg. H₂O occurs, in contrast to the markedly hypotonic urines seen in diabetes insipidus. Such urine concentration, albeit inadequate, represents the conservation of many liters of water. A gradual water deficit and a slowly progressive rise in serum tonicity occur, rather than the copious diuresis and sudden severe dehydration which characterize diabetes insipidus. Probably the clouded sensorium in many of these patients prevents an appropriate expression of the thirst impulse and a properly augmented water intake.

It is conceivable that this very gradual development of a water deficit may. by permitting organism adaptation, provoke the retention of salt. The threat to the integrity of extracellular volume and ultimately plasma volume could initiate the secretion of increased quantities of salt-retaining hormone by the adrenal gland. 81, 82 Leaf and Bartter showed that Pitressin administration and progressive water retention in normal man ultimately evoke a salt-and-water diuresis in the face of a falling plasma electrolyte concentration.88 They attributed this loss of salt to a reduced rate of secretion of the salt-retaining hormone consequent to the gradual expansion of the extracellular volume. phenomenon of salt retention in this form of serum hypertonicity may represent the opposite of the situation studied by these authors, namely, a slowly contracting extracellular volume stimulating the secretion of salt-retaining hormone despite the rising plasma salt concentrations. Why salt retention persists despite the progressive expansion of the extracellular volume to normal and supernormal values is not clear. It is possible that some other stimulus not yet understood initiates the salt retention during the development of this form of serum hypertonicity. Finally, as extracellular salt concentration rises because of the combination of inadequate conservation of water and the retention of salt, water would shift from the cells to maintain osmotic equilibrium.

The data here do not serve as crucial experiments to help delineate the precise mechanism responsible for the development of this syndrome. They seem to support best the hypothesis which places the defect in the central osmoreceptor. In this view a progressive and incomplete form of antidiuretic hormone insufficiency would explain the observed findings. Certainly these data argue that such a syndrome may occur in the face of what is generally an adequate water intake and with the persistence of relatively normal renal function.

SUMMARY

The syndrome of serum hypertonicity secondary to cerebral disease is discussed and an additional case presented. Balance studies were performed during the recovery phase, and a marked salt diuresis in association with maximal urinary concentration was observed. The mechanisms which may explain the syndrome are discussed.

SUMMARIO IN INTERLINGUA

Se presentava le opportunitate de effectuar studios de balancia in un patiente durante su recuperation ab sever hyperosmolaritate seral secundari a meningitis purulente. Durante iste phase recuperatori, non-ingestion de sal esseva mantenite, mesurationes serial del concentrationes de solutos e electrolytos in le plasma esseva effectuate, e le excretion total de urina esseva colligite e analysate pro le concentration de solutos, tanto total como etiam individual. Le phase del retorno a un normal osmolaritate del sero esseva characterisate per (1) un marcatemente positive balancia de aqua, (2) le conservation maximal de aqua con le elaboration de urina de concentration maximal, e (3) un considerabilemente negative balancia de sal, con totales de 600 mEq de chloruro e 800 mEq de natrium. Plure observationes effectuate durante le disveloppamento del hypertonicitate seral reveleva le incapacitate de producer un maximalmente concentrate urina in le presentia de un montante tonicitate del sero. Iste observationes significa que le disveloppamento de iste syndrome es causate per le incapacitate relative de conservar aqua o de producer un urina de appropriate concentrationes in association con un retention considerabile de sal. Iste combination de observationes pare explicar se le melio per un inadequate formation de hormon antidiuretic in consequentia de un progressivemente decrescente sensibilitate del ansa afferente in le reflexo neurogene antidiuretic. In consequentia de iste progressive dissensibilisation, le formation de hormon antidiuretic-ben que illo continua—deveni cumulativemente inadequate. Le menacia del privation de aqua e le reduction de su volumine initia possibilemente le secretion de un hormon haloretenitori, forsan via le glandula adrenal.

BIBLIOGRAPHY

- Allott, E. N.: Sodium and chlorine retention without renal disease, Lancet 1: 1035– 1037, 1939.
- Luetscher, J. A., Jr., and Blackman, S. S., Jr.: Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage, Ann. Int. Med. 18: 741-756, 1943.
- Sweet, W. H., Cotzias, J. C., Seed, J., and Yakovlev, P.: Gastrointestinal hemorrhages, hyperglycemia, azotemia, hyperchloremia and hypernatremia following lesions of the frontal lobe in man, A. Research Nerv. and Ment. Dis., Proc., The frontal lobes 27: 795-822, 1948.

- Peters, J. P.: The role of sodium in the production of edema, New England J. Med. 239: 353-362, 1948.
- Goodale, W. T., and Kinney, T. D.: Sulfadiazine nephrosis with hyperchloremia and encephalopathy, Ann. Int. Med. 31: 1118-1128, 1949.
- Higgins, J., Levin, W., O'Brien, J. R. P., and Taylor, W. H.: Metabolic disorders in head injury, Lancet 1: 1295-1300, 1951.
- MacCarty, C. S., and Cooper, I. S.: Neurologic and metabolic effects of bilateral ligation of anterior cerebral arteries in man, Proc. Staff Meet., Mayo Clin. 26: 185-190, 1951
- Cooper, I. S., and MacCarty, C. S.: Unusual electrolyte abnormalities associated with cerebral lesions, Proc. Staff Meet., Mayo Clin. 26: 354-360, 1951.
- Cooper, I. S., and Crevier, P. H.: Neurogenic hypernatremia and hyperchloremia, J. Clin. Endocrinol. and Metabolism 12: 821-830, 1952.
- Welt, L. G., Seldin, D. W., Nelson, W. P., German, W. J., and Peters, J. P.: Role of the central nervous system in metabolism of electrolytes and water, Arch. Int. Med. 90: 355-378, 1952.
- Zimmerman, B., and Freier, E. F.: The occurrence in surgical patients of severe hypernatremia without exogenous dehydration, Surgery 31: 373-384, 1952.
- Engstrom, W. W., and Liebman, A.: Chronic hyperosmolarity of the body fluids with a cerebral lesion causing diabetes insipidus and anterior pituitary insufficiency, Am. J. Med. 15: 180-186, 1953.
- Ullman, T. D.: Hyperosmolarity of the extracellular fluid in encephalitis, Am. J. Med. 15: 885-890, 1953.
- Schoolman, H. M., Dubin, A., and Hoffman, W. S.: Clinical syndromes associated with hypernatremia, Arch. Int. Med. 95: 15-23, 1955.
- NateIson, S., and Alexander, M. O.: Marked hypernatremia and hyperchloremia with damage to the central nervous system, Arch. Int. Med. 96: 172-175, 1955.
- Levitt, M. F., Turner, L. B. Sweet, A. Y., and Pandiri, D.: The response of bone, connective tissue, and muscle to acute acidosis, J. Clin. Investigation 35: 98-105, 1956.
- Levitt, M. F., Turner, L. B., and Sweet, A. Y.: The effect of experimental venous obstruction on salt and water excretion and renal function in man, J. Clin. Investigation 31: 885-894, 1952.
- Levitt, M. F., and Gaudino, M.: The measurement of extracellular volume in man, Am. J. Med. 9: 208-215, 1950.
- 19. Peters, J. P.: Sodium, water and edema, J. Mt. Sinai Hosp. 17: 159-175, 1950.
- Peters, J. P.: Water balance in health and in disease, in Diseases of metabolism, edited by Garfield Duncan, 1953, W. B. Saunders Company, Philadelphia.
- Brodsky, W. A., and Rapoport, S.: The mechanism of polyuria of diabetes insipidus in man. The effect of osmotic loading, J. Clin. Investigation 30: 282-291, 1951.
- Leaf, A., Mamby, A. R., Rasmussen, H., and Marasca, J. P.: Some hormonal aspects of water excretion in man, J. Clin. Investigation 31: 914-927, 1952.
- Williams, R. H., and Henry, C.: Nephrogenic diabetes insipidus: transmitted by females and appearing during infancy in males, Ann. Int. Med. 27: 84-95, 1947.
- Welt, L. G., Orloff, J., Kydd, D. M., and Altman, J. E.: An example of cellular hyperosmolarity, J. Clin. Investigation 29: 935-939, 1950.
- Anthonisen, P., Hilden, T., and Thomsen, A. C.: Electrolyte disturbances in cerebral lesions, Acta med. Scandinav. 150: 355-367, 1954.
- Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Inactive cell base and the measurement of changes in cell water, Yale J. Biol. and Med. 17: 383-393, 1944.
- Darrow, D. C.: Body fluid physiology. The relation of tissue composition to problems of water and electrolyte balance, New England J. Med. 233: 91-97, 1945.

- Elkinton, J. R., Winkler, A. W., and Danowski, T. S.: Transfers of cell sodium and potassium in experimental and clinical conditions, J. Clin. Investigation 27: 74-81, 1948.
- Verney, E. B.: Antidiuretic hormone and the factors which determine its release, Proc. Roy. Soc., London, s. B. 135: 25, 1947.
- Verney, E. B.: Absorption and excretion of water: antidiuretic hormone, Lancet 2: 781-783, 1946.
- Bartter, F. C., Liddle, G. W., Duncan, L. E., and Delea, C.: The role of extracellular fluid volume in the control of aldosterone secretion in man, J. Clin. Investigation 35: 688-689, 1956.
- 32. Davis, J. O., Howell, D. S., and Southworth, J. L.: Mechanisms of fluid and electrolyte retention in experimental preparations in dogs, Circul. Res. 1: 260-270, 1953.
- Leaf, A., Bartter, F. C., Santos, R. F., and Wrong, A.: Evidence in man that urinary electrolyte loss induced by Pitressin is a function of water retention, J. Clin. Investigation 32: 868-878, 1953.

TUBERCULOMA OF THE BRAIN WITH TUBERCULOUS ADENITIS AND EPIDIDYMITIS*

By Sheldon R. Cogan, M.D., and Johann S. Bornstein, M.D., Chicago, Illinois

The incidence of tuberculoma of the central nervous system has been decreasing markedly over the last half-century, in keeping with the decrease observed in all types of tuberculosis. Autopsy statistics have shown this decrease to be from 50% at the turn of the century to the present 3 to 5% expressed as the percentage of all brain tumors in large case series. 1, 2, 3, 4, 5, 6, 18

The mechanism by which the tubercle bacillus arrives in the central nervous system has been well worked out.^{11, 12, 9} The usual portals of entry to the human organism are the pulmonary and oral routes. The latter has been virtually eliminated as an important source of infection in this country by adequate control of milk-borne disease. There are many instances on record of direct invasion of the central nervous system by extension from contiguous foci in bone or soft tissues; however, almost always the tubercle bacilli arrive at the central nervous system via the bloodstream.⁹ During the formation of the primary complex a stage of hypersensitivity occurs, at which time the tuberculin skin test becomes positive. This is accompanied by a hematogenous spread of bacilli, with deposition of organisms in various tissues throughout the body. Usually these foci go on to heal, but factors may come into play which result in the development of tuberculous disease, such as meningitis or osteomyelitis. Indeed, any organ may be involved.

The factors which determine the course are not all known, but include the number of bacilli lodged in a focus, the relation of the lesion to the blood supply, the natural resistance of the host, the nature of the hypersensitivity reaction,

^{*}Received for publication July 10, 1957.

Requests for reprints should be addressed to Dr. J. S. Bornstein, Chest Department, Michael Reese Hospital, Twenty-ninth Street and Ellis Avenue, Chicago 16, Illinois.

the presence of superimposed infection, stress and strain, pregnancy, and activation of the steroid mechanism. This dissemination at the time of the primary complex is one method of access of the bacilli from an extraneural focus which becomes active at any time after the primary infection. The usual course of the central nervous tissue focus is healing, as is true of most hematogenous foci. However, activity of the brain lesion may follow directly upon deposition of the bacilli, or it may become reactivated at any later date.

It is the purpose of this paper to report a case of intracranial tuberculoma with tuberculous lymphadenitis and epididymitis. This case is of interest because it highlights the relationship of extrapulmonary tuberculosis to intracranial tuberculoma. It presents us with an opportunity to review this relationship and to discuss further the recently altered postoperative prognosis of these cases.

CASE REPORT

A 35 year old Negro male was seen first in the outpatient clinic with the complaint of progressively severe frontal and occipital headache of three months' duration. The patient denied cough, weight loss or exposure to tuberculosis, and was otherwise asymptomatic. The past history was negative except for infectious hepatitis in 1946. The physical examination when the patient was first seen revealed a blood pressure of 130/80 mm. of Hg. There was enlargement of the left supraclavicular and posterior cervical lymph node chains. These nodes were hard, discrete, movable, nontender, and enlarged to 2 cm. in size. A 1-cm. hard nodule was palpated in the right epididymis. The remainder of the general examination was negative. The optic fundi and a careful neurologic survey were negative. The patient was then listed for hospitalization for lymph node biopsy and additional studies. Six days following the initial visit he was admitted to the medical and surgical services of Michael Reese Hospital. The physical findings at this time were unchanged except for the optic fundi. These disclosed bilateral papilledema of two diopters, and numerous flameshaped hemorrhages extending radially from both disc margins. On the second hospital day a left supraclavicular lymph node biopsy was performed. The histologic diagnosis was caseous tuberculosis. Ziehl-Neelsen stain revealed acid-fast bacilli present in the lymph node section. The excised tissue was subsequently positive on culture for tubercle bacilli. On the fifth hospital day the diagnosis of intracranial tuberculoma, tuberculous adenitis and epididymitis was made, and the patient was immediately placed on streptomycin, 1 gm. daily, isonicotinic acid hydrazide, 400 mg. daily, and para-aminosalicylic acid, 12 gm. daily. X-ray studies of the chest revealed only bilateral apical pleural thickening. X-rays of bones and intravenous pyelograms were negative. The blood count, urinalyses and routine blood chemistries were all within normal limits. Three bronchial lavages were negative for tubercle bacilli on concentration and subsequent culture. Because of the risk to the patient's sight engendered by the rapidly increasing intracranial pressure, it was felt that immediate craniotomy should be performed. On the twelfth hospital day he was subjected to ventriculography, which revealed a right parietal lobe lesion. At craniotomy, a well encapsulated, 3.5 by 3.5 by 3 cm. mass was removed from the right parietal lobe. gross picture was that of tuberculoma; microscopic sections showed typical caseation necrosis. The chief concern of those attending the patient at this time was the possible development of tuberculous meningitis; and the dose of streptomycin was accordingly raised to 2 gm. daily. Immediately following surgery a complete left hemiplegia and hemianesthesia were noted. The patient was febrile for the first seven postoperative days (99° to 100° F. orally). Spinal fluid examinations on the tenth and thirtieth postoperative days showed no abnormalities. The hemiplegia

improved only slightly to time of discharge. The sensory functions returned completely. He was discharged on the fifty-second postoperative day to sanatorium care with a 90% left hemiplegia. On the seventeenth hospital day, streptomycin was decreased to 1 gm. daily; isonicotinic acid hydrazide and para-amino salicylic acid remained at the previous dosage level. At the time of discharge he had no clinical evidence of active infection other than the adenopathy and epididymal nodule. His present neurologic status is as described above.

DISCUSSION

Most intracranial tuberculomas do not give rise to symptoms—they are found at necropsy. Symptomatic cases present an expanding intracranial lesion, with or without focal neurologic signs, and are indistinguishable from brain tumor. 14, 15, 16 Vague central nervous system symptoms may be present for a variable period of time before the onset of the above picture. The symptomatology of our case agrees well with that described in the literature. However, our case differed in that evident extrapulmonary sites of tuberculosis were present and were diagnosed, enabling us to make the preoperative diagnosis of intracranial tuberculoma. In the absence of evidence such as this, the diagnosis is made at the time the lesion is examined.

Intracranial tuberculoma may involve any part of the brain substance. Survey of large case series at autopsy shows an apparent predilection for the cerebellum. Statistics indicate cerebellar involvement in from 30 to 40%, the next most common location being the cortical areas. The pons is involved in from 10 to 15%, the basal ganglion in 10%, and the midbrain in from 5 to 10%. Surgical results are best in the cortical areas.⁵

The postoperative prognosis has changed dramatically since the advent of antituberculous chemotherapy. 19, 14, 15, 17 Due to the surgical trauma inherent in the removal of an intracranial mass, tubercle bacilli are strewn along the path of removal, including gross contamination of the meninges. Tuberculous meningitis was a very common complication of surgery for tuberculoma and was almost always fatal. The incidence of this complication was so high that Cushing in 1932 advocated that only decompression be performed in such cases. Reports have appeared recently of postoperative meningitis occurring in only 10 to 20% of cases in which streptomycin alone was utilized as an antibacterial agent. This is in sharp contrast to the almost 100% incidence of meningitis prior to the advent of this drug. With the introduction of combined antituberculous chemotherapy, the prognosis should become better than that reported to date. Isonicotinic acid hydrazide appears to be the most potent of the newer drugs in its action on the meninges. Schwartz 17 reported on three cases of intracranial and one case of spinal epidural tuberculoma that received postoperative streptomycin, isonicotinic acid hydrazide and para-aminosalicylic acid. One case died a surgical death; the others did not develop tuberculous meningitis. However, the case follow-up was of short duration.

We have commented on tuberculous meningitis as a surgical complication of intracranial tuberculoma. At this point we would like to make some general comments as to the relationship of these two disease entities. Rich and Mc-Cordock ¹⁸ concluded from animal experimentation that hematogenous seeding of the meninges was not responsible for the development of tuberculous meningitis. They found that they could not produce meningitis by intravenous admin-

istration of bacilli. They surveyed 82 cases of tuberculous meningitis at autopsy and in 88% they found a focal caseous lesion older than the meningitis which was in communication with the subarachnoid space. They felt that these lesions, by breakdown and direct contamination of the meninges, had caused the inflammatory process. MacGregor in 1937 11 conducted experiments on animals and performed an autopsy survey designed to evaluate Rich's concept. His conclusions were in direct agreement with those of Rich. In 88 cases of tuberculous meningitis he found 59 brain lesions which definitely and six which probably were in such a location as to have caused meningeal contamination. Arguing against Rich's concept, MacGregor stated that 83% of his cases had miliary tuberculosis. However, he felt that in these cases the hematogenous spread probably antedated and gave rise to the cerebral lesion which caused the meningitis. He also observed 24 cases of nonmiliary tuberculosis without meningitis. Eleven had lesions of the central nervous system, and in three these were the only hematogenous foci. He concluded from this observation that hematogenous lesions could be set up in the central nervous system as a result of a minor dissemination of bacilli which produced no other foci.

There are few reports in the English literature which deal with the relationship of intracranial tuberculoma and other extraneural sites of tuberculosis. In 1933 Jaffe and Schultz,9 working at Cook County Hospital, surveyed 48 cases of autopsy-proved intracranial tuberculosis. Thirty-two cases were associated with acute miliary tuberculosis which, they felt, arose either at the time of the primary complex or at a later time as the result of an exacerbation of a previously quiescent lesion. Sixteen cases had apparently isolated intracranial tuberculoma. Of these, eight had also pulmonary tuberculosis which was clearly of a longer duration than the brain lesions. In seven cases the autopsy findings suggested that lymph node tuberculosis, location unspecified, was responsible for the earlier hematogenous spread to the brain. Two cases had tuberculous salpingitis, and in one case they felt the intracranial lesion was secondary to adrenal involvement. In one, genitourinary tuberculosis of long standing was found. Every case had at least one extraneural focus of tuberculosis. Asenjo.14 working in Chile, evaluated 159 cases of intracranial tuberculoma and found that 86 presented clinical evidence of extraneural tuberculosis, and of these, 42 had pulmonary disease. At autopsy, an additional 20 disclosed pulmonary tuberculosis.

The accompanying diagrams summarize the clinical and postmortem incidence of extraneural tuberculosis in cases of intracranial tuberculomas as reported in the English literature. Figure 1 contains a compilation of 331 autopsied cases. In 127 cases the lymph node involvement found was chiefly mediastinal and retroperitoneal. Pulmonary tuberculosis was present in 61 cases, miliary involvement in 36, genitourinary in 13, peritoneal in eight, gastrointestinal in eight, bone in five, liver and mastoid in four, spleen and adrenal in three, and two cases had tuberculous salpingitis. This is contrasted with figure 2, in which the extraneural tuberculosis was diagnosed on clinical grounds. Of a total 178 cases, extraneural tuberculosis was found in 93 locations. The site was unspecified in 45 cases; 43 were in lung, two in lymph nodes, two in bone, and one was epididymal.^{9, 14, 7, 10, 15, 18}

From the foregoing data it is apparent that intracranial tuberculoma is part of a widespread heavy dissemination of tubercle bacilli occurring in the immediate

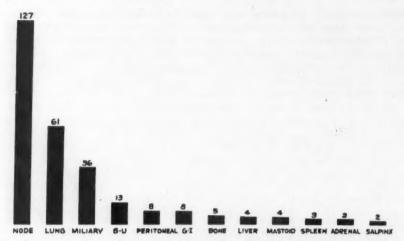


Fig. 1. Three hundred thirty-one autopsied cases of intracranial tuberculoma listed as to the number of specified extraneural sites of tuberculosis.

or remote past. From the diagnostic standpoint, this understanding as to the pathogenesis of these lesions has a twofold significance. The first is that, in patients presenting with the clinical syndrome of a space-occupying intracranial lesion and a known site of extrapulmonary tuberculosis, the presence of intra-

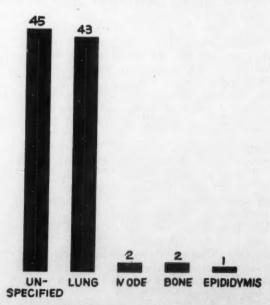


Fig. 2. One hundred seventy-eight cases of intracranial tuberculoma listed as to extraneural sites of tuberculosis diagnosed clinically.

cranial tuberculoma will be far more common than in patients presenting with the cerebral picture and evidence of pulmonary tuberculosis. Evidence for this may be adduced by comparing the relatively low incidence of intracranial tuberculoma in cases of pulmonary tuberculosis with the high incidence of systemic tuberculosis in patients with cerebral lesions.

The second point of clinical importance follows from the great incidence of extrapulmonary disease seen in patients with intracranial tuberculoma. As has been stated, it is believed that these lesions arise as a result of a heavy, widespread dissemination which is acted upon by a number of factors, as outlined previously. These patients, as is the case with patients presenting evidence of any other extrapulmonary tuberculosis, are especially prone to develop additional systemic lesions. A diligent search should be made for these foci, and periodic checks should be made for the remainder of the lives of these individuals.

By far the most important consideration in the postoperative management of intracranial tuberculoma is the prevention of tuberculous meningitis. The outlook is extremely good with the utilization of combined antituberculous chemotherapy. It is our opinion that these patients should be treated with streptomycin, para-aminosalicylic acid and isonicotinic acid hydrazide, with the latter felt to be the most potent single agent. This program should be carried out with streptomycin for one and one-half years, and isonicotinic acid hydrazide and para-aminosalicylic acid for from two to three years, depending upon the individual case.

Sibley and O'Brien ¹⁹ recommended that specific antimicrobial therapy be given for a period of from 60 to 90 days postoperatively. Their thinking is outmoded by present day standards. The possibility of drug toxicity and bacterial resistance which they stress must be waived in view of the danger of tuberculous meningitis and the presence of other extraneural lesions. We feel that prolonged therapy, particularly with isonicotinic acid hydrazide, may be needed for from two to three or more years because of the possibility of reactivation after the cessation of prolonged chemotherapy. The day of short antimicrobial therapy is gone. The prolonged therapeutic regimen will serve to decrease the incidence of meningeal complications, and will also serve to control other extrapulmonary lesions which are present in high incidence whether demonstrable or not. The use of intrathecal streptomycin has been favored by the English and French workers but has not been found to be advantageous by the American school.

SUMMARY

- 1. The incidence of intracranial tuberculoma has decreased markedly over the last half-century, paralleling the decrease in tuberculosis in general. This is related to better living standards, effective chemotherapeutic agents, intensive case finding surveys, and a better understanding as to the pathogenesis of the disease.
- 2. The pathogenesis of intracranial tuberculoma is believed to be secondary to hematogenous spread of the bacilli, either at the time of the primary complex or at a later time, due to reactivation of a previously quiescent lesion. Activity of the central nervous system lesion, as in lesions at other sites, depends upon a number of factors, which have been enumerated.

3. A case, diagnosed preoperatively, of intracranial tuberculoma with tuberculous adenitis and epididymitis is presented.

4. The usual presenting symptoms of a clinically significant intracranial tuberculoma are those of an expanding intracranial lesion, with or without focal

neurologic signs.

5. Prior to the advent of streptomycin, the postoperative incidence of meningitis was practically 100%, and it was uniformly fatal. This has dropped to an incidence of from 10 to 20% with streptomycin, and the outlook for the future is even better with more recently developed chemotherapeutic agents, especially isonicotinic acid hydrazide.

6. It is felt that tuberculous meningitis usually results from contamination of the meninges by breakdown of a continuous lesion within the brain which

was present before the development of the meningitis.

7. The preoperative diagnosis of intracranial tuberculoma in patients with expanding intracranial lesions may be made if there is evidence of additional extrapulmonary tuberculosis. This is of importance in allowing chemotherapy to be started preoperatively.

8. The preoperative antimicrobial therapy is emphasized.

9. Patients with intracranial tuberculoma should be periodically checked

for development of other extrapulmonary lesions.

10. To prevent the postoperative meningitis as well as to treat occult sites of tuberculosis, long-term chemotherapy for at least two and probably three years should be carried out in these patients following surgery.

SUMMARIO IN INTERLINGUA

Le necropsias indica que le incidentia de tuberculoma del systema nervose central ha diminuite in le curso del passate 50 annos.

Bacillos tubercular arriva in le systema nervose central quasi exclusivemente via le circulation de sanguine. Usualmente iste dissemination hematogene occurre durante le formation de un primari complexo pulmonar in association con un stadio de hypersensibilitate. Le resultante focos in le systema nervose central es usualmente resanate de maniera spontanee, in dependentia de factores bacterial e de factores in le hospite. Post le infection primari re-infection o re-activation pote occurrer in responsa a un foco extraneural, con invasion del circulation de sanguine e affection

del systema nervose central.

Es reportate le caso de un masculo negre de 35 annos de etate qui habeva, depost tres menses, sever formas de mal de capite frontal e occipital. Ille habeva un nodulo dur in le epididymis dextere. Dur nodos lymphatic se trovava in le catena posterocervical e in le catena sinistro-supraclavicular. Esseva presente le syndrome de un crescente lesion intracranial. Biopsia de nodo lymphatic sinistro-supraclavicular revelava caseose focos tuberculotic. Tincturation secundo Ziehl-Neelsen demonstrava le presentia de bacillos acido-resistente in sectiones histologic. Plus tarde, le nodo lymphatic produceva un cultura positive pro Mycobacterium tuberculosis. Ante le effectuation de craniotomia, indicate per observationes diagnostico-ventriculographic, le patiente recipeva streptomycina (1 g per die), oral hydrazido de acido isonicotinic (400 mg per die), e acido para-aminosalicylic (12 g per die). Ab le lobo dexteroparietal, un massa caseose de un grandor de 3,5 per 3,5 per 3,0 cm esseva excidite. Le patiente disveloppava hemiplegia e hemi-anesthesia sinistre. Le dosage de streptomycina esseva augmentate a 2 g per die, administrate per via intramuscular, pro prevenir le supervention de meningitis. Plus tarde un medication de mantenentia esseva

establite, consistente de doses diurne de 1 g de streptomycina, 400 mg de hydrazido de acido isonicotinic, e 12 g de acido para-aminosalicylic in administrationes oral.

Ante le advento de specific therapias antituberculotic, le excision de un tuberculoma intracranial haberea essite sequite per meningitis e morte. Con le uso de streptomycina sol, complicationes post-meningitic ha decrescite ab un incidentia de quasi 100 pro cento a un incidentia de circa 10 a 20 pro cento. Con le uso combinate de streptomycina, hydrazido de acido isonicotinic, e acido para-aminosalicylic, ille incidentia se ha reducite ancora plus.

Clinicamente, tuberculomas intracranial pote remaner silente durante longe periodos de tempore. Post lor activation, illos presenta usualmente le syndrome de un crescente lesion intracranial, simile a un tumor non-tuberculotic.

Le cerebello es interessate in inter 30 e 40 pro cento del casos, secundo un extense serie de necropsias. Le ponte es interessate in inter 10 e 15 pro cento, le ganglios basal in 10 pro cento, le cerebro central in inter 5 e 10 pro cento. Affectiones cerebral seque affectiones cerebellar ab un puncto de vista procentual. Le relation inter tuberculoma intracranial e meningitis tuberculotic, secundo le investigationes de Rich e McCordock e etiam de MacGregor e Green, es que previe lesiones cerebral es frequentemente le causa de meningitis.

Extraneural focos tuberculotic in casos de tuberculose intracranial es commun. Ex un serie de 331 casos de tuberculoma, 274 esseva associate con tuberculose extraneural. In multes de iste casos, le loco del tuberculose esseva retroperitonee o mediastinal. Altere locos de marcate frequentia esseva le pulmones, le vias genito-urinari, le vias gastro-intestinal, le ossos, le hepate, le splen, e le tubo fallopian.

Tuberculose intracranial es un parte del extense dissemination de bacillos tuberculotic que ha occurrite in le passato immediate o remote.

BIBLIOGRAPHY

- 1. Davis, L.: The principles of neurosurgery, 2nd Ed., 1942, Lea and Febiger, Philadelphia.
- 2. Starr, M. A.: Tumors of the brain in children, M. News 54: 29, 1889.
- 3. Tooth, W. H.: Observations on intracranial tumors, Brain 35: 61, 1908.
- 4. Toimis, W.: Uber Hirngeschwulste, Ztschr. f. d. ges. Neurol. u. Psychiat. 101: 114, 1896.
- 5. Wilson, K.: Neurology, 1940, Wm. Wood and Company, Baltimore.
- Van Wagener, W. P.: Tuberculoma of the brain: incidence among intracranial tumors and surgical aspects, Arch. Neurol. and Psychiat. 17: 51, 1927.
- Anderson, F.: Tuberculoma of the central nervous system, Arch. Neurol. and Psychiat. 20: 354, 1928.
- 8. Ferris, H. W.: Eight cases of tuberculoma of the brain at autopsy, J. A. M. A. 92: 1670, 1929.
- Jaffe, H. L., and Schultz, W.: The relationship between tuberculoma of the central nervous system and tuberculosis of other organs, Am. Rev. Tuberc. 33: 302, 1936.
- Garland, H. G., and Armitage, G.: Intracranial tuberculoma, J. Path. and Bact. 37: 461, 1933.
- MacGregor, A. R., and Green, J. P.: Tuberculosis of the central nervous system with special reference to tuberculous meningitis, J. Path. and Bact. 45: 613, 1937.
- 12. Buchstein, H. F.: Tuberculoma of the brain, Arch. Neurol. and Psychiat. 43: 635, 1940.
- Bernstein, T. C., Krueger, E. G., and Nayer, H. R.: Tuberculoma of the brain, Am. Rev. Tuberc. 62: 654, 1950.
- Asenjo, A., Valladares, H., and Fierro, J.: Tuberculoma of the brain, Arch. Neurol. and Psychiat. 65: 146, 1951.
- 15. Revilla, J.: Intracranial tuberculoma, J. Neurosurg. 9: 555, 1952.
- Descunset, P., Garre, H., and Pheline, L.: Tuberculoma of the brain and cerebellum, J. Neurosurg. 11: 244, 1954.

- Schwartz, M., Gilman, R. A., Robey, J. S., Settle, J., and Paddock, L. E.: Tuberculomas
 of the central nervous system: review and report of four cases successfully managed
 with surgery and chemotherapy, Ann. Int. Med. 42: 1076-1088 (May) 1955.
- Rich, A. R., and McCordock, H. A.: The pathogenesis of tuberculous meningitis, Bull. Johns Hopkins Hosp. 52: 5, 1933.
- Sibley, W. A., and O'Brien, J. L.: Intracranial tuberculomas: a review of clinical features and analysis of present day treatment, Arch. Neurol. and Psychiat. 74: 333, 1955.

TOXIC HEPATIC NECROSIS (HEPATITIS) DUE TO ISONIAZID: REPORT OF A CASE WITH CIRRHOSIS AND DEATH DUE TO HEMORRHAGE FROM ESOPHAGEAL VARICES*

By A. Donald Merritt, M.D., Bethesda, Maryland, and Bernard F. Fetter, M.D., Durham, North Carolina

Although isoniazid is an excellent drug in the therapy of tuberculosis, it does give rise to toxic reactions in some 5% of patients.¹ The first, more common type of reaction is seen in the nervous system and is manifested by various peripheral neuritides. This toxic effect is apparently related to the pharmacologic action of the drug, and varies in incidence and severity with the dosage.²,³ The second, less common group of reactions is felt to be allergic in nature,⁴,⁶ with the varied patterns of dermatitis,¹ drug fever,⁴,ⁿ,² leukopenia, purpura¹ and hepatitis.⁶,⁰,¹¹ Hepatitis is most unusual, having been reported in the English literature in only four patients. All four were jaundiced, but none was reported as having permanent liver damage. In the present report, however, severe cirrhosis, esophageal varices, hemorrhage and death followed the prolonged administration of isoniazid, coupled with the failure to recognize hepatic necrosis secondary to its use on two occasions.

This case is reported to emphasize the consequences of unrecognized drug reactions, as well as a rare reaction to isoniazid, and to demonstrate the effectiveness of hyposensitization to isoniazid, which is a practical and useful procedure should continuation of therapy with the drug be necessary.

CASE REPORT

A 38 year old married white woman was admitted to Duke Hospital on September 28, 1956, with thoracic back pain and inability to walk because of paraparesis. In 1940 and 1944 she had received arsenical therapy for systemic and central nervous system syphilis. In 1946 she had been seen in the Duke Out-patient Clinic with back pain radiating to the left leg. Her physical examination was normal. A positive serologic test for syphilis in a titer of 14 was the only laboratory abnormality. She was next seen in 1949 with persistent low back pain radiating to the thighs. Her liver was palpable 5 cm. below the right costal margin at that time.

^{*} Received for publication July 19, 1957.

From the Departments of Medicine and Pathology, Duke University School of Medicine, Durham, North Carolina.

Requests for reprints should be addressed to A. Donald Merritt, M.D., National Institutes of Health, NIAMD, Room 8N252, Bethesda 14, Maryland.

X-rays of the chest, hips and lumbar spine were normal. No cause for her back pain was found, and when seen four weeks later she was much improved.

In 1951, when the patient was admitted to another hospital, her back pain had returned but other findings were unchanged. Four years later (1955) she was readmitted to the same hospital with increasing back pain, now located in the midthoracic region and radiating to both legs. Spinal x-rays then revealed collapse and fracture of the eleventh and twelfth thoracic vertebrae. Urine and gastric contents were negative for tuberculosis. Since she was thought clinically to have tuberculosis of the spine, she was transferred to a sanatorium for further treatment and spinal fusion. The latter procedure was canceled when the patient developed precordial pain and tachycardia during the preanesthetic period. The patient was put at rest in bed, and isoniazid, 300 mg., and para-aminosalicylic acid, 12 gm., were administered daily, with streptomycin, 1 gm. twice a week. After 37 days of drug therapy she developed a rash. Ten days later she received a blood transfusion, followed in two days by clinical jaundice which persisted until her discharge 37 days later, on December 20, 1955. (See table 2 for pertinent laboratory studies.) Though the diagnosis was not proved, she was thought to have tuberculosis of the spine with superimposed infectious hepatitis. Antituberculous drug therapy was continued until her discharge.

The patient remained at home without therapy until her admission to Duke Hospital in 1956. There had been a slight decrease in sensation in her legs and genital numbness for several months. Also, she had noted a 30-pound loss of weight during the year prior to admission. Her past and family history revealed no contact with tuberculosis.

At the time of admission she was afebrile and had a blood pressure of 100/70 mm. of Hg. She was obese and appeared chronically ill. The skin was dry, and there was reddening of the fingertips and palms. Bilateral healed scars of the tympanic membrane were present, with partial deafness of the conduction-type. The anterior-posterior diameter of the chest was increased, with a sharply pointed, tender, gibbous deformity of the midthoracic spine. Moist râles were heard at the base of the right lung. The heart was normal. A firm, nontender spleen and liver were palpable 5 cm. below their respective rib margins. Hypesthesia below the level of the eleventh thoracic vertebra and decreased vibration and position sense below the knees were noted on neurologic examination. The abdominal reflexes were absent. In the upper extremities the deep tendon reflexes were normal, but they were decreased in the right lower extremity and absent in the left lower extremity. Plantar responses were flexor. The patient was unable to walk because of marked weakness and muscle wasting in both lower extremities.

Laboratory data are summarized in table 1. X-rays demonstrated pleural thickening and a small amount of fluid at the right costophrenic angle. There were destruction, collapse and angulation of the tenth, eleventh and twelfth thoracic and the first lumber vertebrae. A barium swallow obtained on the fortieth day of hospitalization revealed a normal esophagus with no evidence of varices. Pleural fluid, aspiration of bone marrow and, later, surgical drainage of a paravertebral abscess in the area of her gibbous deformity were culturally diagnostic of tuberculosis.

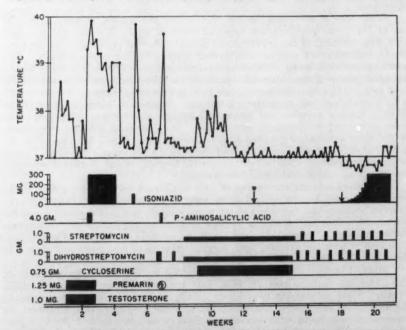
Figure 1 outlines the patient's clinical course from the time of her admission to Duke Hospital on September 28, 1956, until her discharge on February 21, 1957. Premarin * and testosterone were given initially as treatment for osteoporosis. In the absence of information concerning her previous hospitalizations, treatment for tuberculosis was begun with isoniazid and para-aminosalicylic acid 16 days after admission. The patient immediately developed a high fever and was suspected of having a drug reaction. Because isoniazid was considered to be an essentially non-

^{*} Premarin: Ayerst Laboratories conjugated equine estrogens.

TABLE 1 Laboratory Data (S. C.)

| | 7-6-55 | 10-28-55 | 11-14-55 | 12-5-55 | 9-29-56 | 10-17-56 | 10-24-56 | 10-29-56 | 10-31-56 | 11-5-56 | 11-12-56 | 12-3-56 | 1-4-57 | 2-16-57 |
|--|---|----------------------------|--|--|--------------------------------|-----------------------------------|---|-------------------------------------|--|---|---|--|--|---|
| Hemoglobin (gm.%) Hematocrit (%) WBC X109 Urine bile Bilirubin (mg.%) Alk. phos. (Bodansky u.) Total protein (gm.%) Albumin (gm.%) Globulin (gm.%) Thymol flocculation Thymol turbidity (units) Cholesterol (mg.%) | 10.7 7.6 4.6 8.4 4.3 4.1 | 10.0 8.0 0.12 1.1 | 11.6 36 9.0 \$\frac{1}{4} + \frac{1}{6.0} | 10.4 36 8.5 19.0 4+ 125 40 | 37 7.2 7.3 2.3 5.0 | 4.7 0 1.4 0 2.8 74 | 11.2 33 9.3 + 8.8 1.0 2+ 8.0 65 | + 10.7 2.8 3+ 7.5 46 | 7.4 9.0 1.7 7.3 3+ 7.5 200 | 10.3 33 · 7.4 + 5.6 3.1 8.8 1.6 7.2 3+ 4.0 | 7.1 3.4 4.3 8.7 2.0 6.7 3+ 4.0 | 2.0 5.2 9.0 1.5 7.5 3+ 7.5 | 10.5 31 5.6 1.5 9.1 1.5 7.6 4+ 9.0 | 37 5.0 1.2 3.5 9.2 2.0 7.2 1+ 3.5 |

toxic drug and important in her therapy, this medication was continued until jaundice became evident 12 days later. A needle biopsy of the liver obtained at this time was reported as showing postnecrotic cirrhosis. Following discontinuance of isoniazid the patient became afebrile. However, she developed a prompt febrile response when given an oral dose of this drug seven days later. Ten days later she received dihydrostreptomycin, without reaction. On the following day an oral dose of para-aminosalicylic acid elicited a prompt febrile response. Again all drugs were



 Ψ · · · Ψ * Subcutaneous isoniazid was begun with 0.1 mg. with daily increments of 0.1 mg. to 1.0 mg. followed by Ψ · · Ψ 1.0 mg. increments to 10.0 mg. Oral dasage was begun with 12.5 mg. and increased as charted.

Fig. 1. Clinical course and treatment.

discontinued. Six days later she was begun on therapy again, with dihydrostreptomycin followed by streptomycin, without reaction. At the time of surgical drainage of her paravertebral abscess, cycloserine was begun as an adjunct to streptomycin therapy. With operation she developed a low grade fever which persisted for 16 days.

It was considered important that isoniazid be utilized in this patient's therapy. First, patch tests were done with both para-aminosalicylic acid and isoniazid, with negative results. Shortly thereafter, hyposensitization with isoniazid was begun via the subcutaneous route. There were no untoward reactions, and the patient was discharged from the hospital with a back brace, to be re-admitted for definitive orthopedic therapy after several months of antituberculous treatment. At the time of discharge (February 21, 1957), she was receiving isoniazid, 300 mg. daily, and streptomycin, 1 gm. twice a week, with no evidence of a drug reaction.

Four days after discharge from Duke Hospital she was admitted to a local hospital with massive hemorrhage from esophageal varices. With transfusions and supportive therapy she recovered and was discharged on April 4, 1957, receiving isoniazid and streptomycin. Her liver function tests were unchanged. On May 11, 1957, she was again admitted to her local hospital with massive bleeding from esophageal varies, and died on May 15, 1957. An autopsy revealed hemorrhage from esophageal varies secondary to cirrhosis. The liver weighed 1,000 gm. and had marked scarring. Figure 2 is a photomicrograph of a representative section revealing fibrosis and distortion such as are seen after toxic hepatocellular damage. Other findings were splenomegaly (540 gm.) and tuberculous osteomyelitis of the thoracic vertebrae.

DISCUSSION

Drug allergy arises in unexpected forms. Multiple sensitivities to drugs are not uncommon and on two previous occasions have been reported to occur with isoniazid and para-aminosalicylic acid. Our patient had a febrile reaction to isoniazid and para-aminosalicylic acid, but it was felt that isoniazid was the drug responsible for her liver destruction. Although these drugs were originally administered without arousing suspicion of their toxicity, when she next received them, there was no doubt that her clinical jaundice progressed with isoniazid administration and subsided with its discontinuance. A febrile reaction was seen to a single dose of para-aminosalicylic acid, but instead of further evidence of liver dysfunction, there was a steady fall in her serum bilirubin and clinical improvement. Para-aminosalicylic acid was therefore not considered to be the offender.

A note in the American Trudeau Society Reports of 1953 ¹ suggested that desensitization to isoniazid might be effective. In 1954 Rothstein and Bruce ¹¹ reported two patients with gastrointestinal symptoms due to isoniazid. Oral desensitization was carried out, with tolerance developing to the drug. While the present patient was hospitalized, Brown et al. ⁶ reported two cases of isoniazid sensitivity in whom desensitization had been accomplished.

Several interesting facets are illustrated by this patient's course which reemphasize the need for thorough drug histories and the confusion which drug therapy may add to an otherwise uncomplicated illness. Information regarding the patient's previous hospitalizations and drug therapy was not available at the time treatment was begun. An immediate reaction to isoniazid and para-aminosalicylic acid was unexpected and was not consistent with the usual period of two to six weeks of drug ingestion prior to a reaction such as fever. It was

thought that some other drug might explain such a febrile response, and for this reason all drugs were discontinued except isoniazid, which was not suspected as the offending agent. Isoniazid was continued uninterruptedly for an additional 11 days, during which time the patient remained febrile and evidenced hepatocellular disease by a rising serum bilirubin and thymol turbidity (table 1).



Fig. 2. Representative section of liver (magnification 35 ×, Masson stain) showing broad zones of fibrous tissue with persistent bile ducts and diffuse lymphocytic infiltration. The small nodules of surviving liver parenchyma show little evidence of regeneration. The paler areas in the parenchyma represent acute necrosis, which is probably related to death from exsanguination.

With the development of jaundice, isoniazid was discontinued and the temperature fell to normal. At this time, records of the patient's previous hospitalizations were received. Review of these records (from which the laboratory data on October 28, November 14 and December 2, 1955, are derived) indicated that she had probably reacted adversely to isoniazid during her earlier hos-

pitalization, and that the illness which had been construed as infectious hepatitis or jaundice two days after transfusion was more likely a reaction to isoniazid.

The patient's drug therapy was tolerated for 37 days before the first manifestation of an adverse reaction—a rash—appeared. This was followed in 12 days by the development of jaundice. Isoniazid and para-aminosalicylic acid were continued an additional 37 days, with persistence of a severe jaundice and laboratory evidence of hepatocellular disease at the time she discharged herself from the hospital. With this information in hand the offending drug was exposed. Patch tests with isoniazid and para-aminosalicylic acid were performed in several strengths without reaction, but when the drugs were given orally (figure 1) a marked febrile reaction to both isoniazid and para-aminosalicylic acid occurred.

It was considered therapeutically important that the patient receive isoniazid in combination with streptomycin as treatment for her tuberculosis of the spine and other evidences of disseminated tuberculosis. As hyposensitization to isoniazid had been previously reported, 5, 10 this was attempted. The more conservative approach of Brown et al. 6 was chosen for this patient who had reacted so severely to isoniazid. Very dilute solutions of isoniazid were injected subcutaneously in gradually increasing strengths (figure 1). During the period of hyposensitization the patient's significant laboratory examinations were carefully carried out. There was a steady decrease in her serum bilirubin and a slower decrease in her thymol indices. She remained afebrile throughout this period, and no other complications were noted. She steadily improved and was tolerating isoniazid in a dosage of 300 mg. daily at the time of discharge. Her subsequent course and death from bleeding esophageal varices confirmed the presence of severe cirrhosis.

In the analysis of this patient's history for the cause of her liver damage, the importance of isoniazid is readily apparent. Subsequent to arsenical therapy there was no evidence of hepatic dysfunction. In 1955, just prior to the use of chemotherapy for tuberculosis, her laboratory studies indicated a normally functioning liver. The probability of infectious hepatitis as the cause of hepatic injury is remote considering the immediate febrile reaction and jaundice when isoniazid was re-administered. The pathologic findings are consistent with massive hepatic necrosis due to a toxic agent.

SUMMARY

A case is presented of hepatic cirrhosis and death from bleeding esophageal varices believed to be secondary to administration of isoniazid. Though the patient had received para-aminosalicylic acid during her initial therapy, and subsequently was shown to have a febrile response to a single oral dose, there was no evidence of hepatocellular damage from this drug.

Hyposensitization to isoniazid was accomplished without complications.

ACKNOWLEDGMENT

I wish to thank Dr. Weldon H. Jordon, who supplied the clinical summary of this patient's last hospital admissions, and Dr. George F. Cameron, who performed the autopsy and sent us a portion of the liver for additional study.

SUMMARIO IN INTERLINGUA

Iste patiente, un femina de racia blanc de 38 annos de etate, suffrente de dolores dorsal e paraparesis in consequentia de osteomyelitis tuberculotic del spina dorsal, disveloppava febre immediate e sever injurias hepatic como resultato de therapia a isoniazido. Esseva constatate plus tarde que illa habeva recipite streptomycina, isoniazido, e acido para-aminosalicylic un anno previemente a un altere hospital. Durante le therapia initial con iste drogas, nulle manifestation toxic occurreva durante cinque septimanas. Postea se disveloppava un eruption, febre, e jalnessa clinic. Proque iste symptomas esseva considerate como effectos de hepatitis infectiose, le uso del drogas esseva continuate usque septe septimanas plus tarde quando illa quitava le hospital, ancora con jalnessa. Isto explica le reactiones immediate a isoniazido e acido para-aminosalicylic al hospital Duke.

Isoniazido esseva considerate como importante in le therapia de iste patiente, e hyposensibilisation esseva effectuate sin complicationes. Illa esseva dimittite, recipiente un therapia de streptomycina e isoniazido, sin indicios de pharmaco-reactiones. Su morte duo menses e medie plus tarde esseva causate per repetite hemorrhagias ab varices esophagee.

Le curso clinic del patiente (tabula 1) e le datos laboratorial (tabula 2) pare indicar que le isoniazido esseva responsabile pro le fibrose hepatic e le distorsion e necrose massive que esseva constatate al necropsia. Le observationes microscopic esseva explicabile como effectos de un agente de toxicitate hepatocellular.

Reactiones toxic a isoniazido es reportate in circa 5% del patientes tractate con ille droga. Neuritis peripheric es le plus commun e pare esser relationate al action pharmacologic del droga. Le reactiones minus commun—dermatitis, febre, leucopenia, purpura, e hepatitis—es considerate como de natura allergic. Hepatitis se trova reportate quatro vices in le litteratura de lingua anglese. Tamen, in nulle del quatro reportos es trovate le constatation de permanente injurias hepatic, como esseva le caso in le patiente del presente reporto.

BIBLIOGRAPHY

- American Trudeau Society: The toxicity of isoniazid: a report of the Committee on Therapy, Am. Rev. Tuberc. 68: 302, 1953.
- Biehl, J. P., and Vilter, R. W.: Effect of isoniazid on vitamin B₀ metabolism; its
 possible significance in producing isoniazid neuritis, Proc. Soc. Exper. Biol. and
 Med. 85: 389, 1954.
- Biehl, J. P., and Nimitz, J.: Studies on the use of a high dose of isoniazid. I. Toxicity studies, Am. Rev. Tuberc. 70: 430, 1954.
- Kalbian, V.: Isonicotinic acid hydrazide hypersensitivity with pyrexial reaction: report of a case, Tubercle 35: 221, 1954.
- Mellette, S. J., and Agress, H.: Toxic reactions to PAS and isoniazid accompanied by leukopenia and atypical lymphocytosis, Am. Rev. Tuberc. 69: 824, 1954.
- Brown, H., Goldstein, G., and Chapman, G.: Allergy to isoniazid: successful immunization in two cases, Am. Rev. Tuberc. 74: 683, 1956.
- Walsh, J. J., Lynn, R. H., and Derbes, V. J.: Pyrexia due to isonicotinic acid hydrazide, J. Allergy 27: 548, 1956.
- Krasmitz, A.: Drug fever due to administration of isoniazid, Am. Rev. Tuberc. 68: 249, 1953.
- Randolph, H., and Joseph, S.: Toxic hepatitis with jaundice occurring in a patient treated with isoniazid, J. A. M. A. 152: 38, 1953.
- Gellis, S. N., and Murphy, R. V.: Hepatitis following isoniazid, Dis. of Chest 28: 462, 1955.
- 11. Rothstein, E., and Bruce, T. H.: Management of isoniazid intolerance, J. A. M. A. 155: 745, 1954.

VICARIOUS BLEEDING *

By FEDERICO DIÉZ RIVAS, M.D., F.A.C.P., Santurce, Puerto Rico

ALTHOUGH extragenital bleeding in women is known to occur, simultaneous bleeding from the eyes, ears, nose, urethra and rectum in association with the menstrual cycle appears to be very rare. Review of the literature fails to reveal a similar case, and because of its uniqueness this case report is presented.

In 1884 Duncan, in a lecture before the London Society of Medicine, said: "It is high time to give up the whole disease as a tissue of error if not of absurdity. I have all my life been on the lookout for a case of vicarious menstruation, but I have never seen an example and never expect to." Eighteen years later Claiborne 2 reported a case of symmetric hemorrhagic spots under each eye in a 16 year old Iewish girl that would develop two or three days before each menstrual period. These red spots would finally ooze blood and form a crust. In 1916 Condit a reported a case of extragenital bleeding from a nevus located over the left ninth intercostal space associated with the menstrual periods. In 1920 Roth reported vicarious menstruation from several sources, epistaxis being the most frequent type encountered among the 255 cases studied. Hemoptysis several days prior to menstruation was recorded on a few occasions. Kieser 5 has reported hemorrhages from the nose, rectum, lungs and urinary bladder. Saitz observed hematomas near the trigone of the urinary bladder during the menses. Frank has described subcutaneous hemorrhages on the flexor surfaces of the thighs and forearms.

Various gynecologists have observed that a hemorrhagic tendency exists prior to and during the menses. An actual increase in bleeding has been observed during operations performed at this period of the cycle. Further evidence of circulatory, electrolyte and tissue changes is demonstrated by the frequency of premenstrual edema of the ankles or puffiness of the eyelids. Slight changes in the voice have been noted regularly by singers, apparently secondary to increased vascularity and edema of the vocal cords. According to Wolff,8 the migraine and tension associated with menstruation are due to intracranial vascular dilatation. Koch, Escher and Lewis 9 recently reported that the bleeding in hereditary hemorrhagic telangiectasia appears commonly five days prior to the menses, and was prevented in several cases by small doses of estrogens or androgens.

CASE REPORT

The patient, a 33 year old white married female, was referred to the School of Medicine, School of Tropical Medicine, on August 31, 1949, by the Morovis Health Unit with the diagnosis of varices of the lacrimal duct or a possible blood dyscrasia. During the previous year she had been having recurring, periodic episodes of bleeding from both eyes, ears and nose. The initial hemorrhage was an epistaxis that lasted

^{*}Received for publication July 22, 1957.

Presented at the Regional Meeting of The American College of Physicians, Puerto Rico Chapter, October 26, 1956.

From the Department of Internal Medicine, University of Puerto Rico, School of Medicine.

Requests for reprints should be addressed to Federico Diéz Rivas, M.D., Professional Building, PDA. 22, Santurce, Puerto Rico.

from five to seven days and was accompanied by severe headache extending from the frontal area to the occiput, dizziness and cold skin. These hemorrhages recurred with each menstrual period, regardless of the remedies used. At the onset of this condition the bleeding episodes coincided with menstruation, but more recently they had seemed to occur also before or afterwards, usually two or three days pre- or postmenstrually. Bleeding had always been more frequent through the eyes and was always preceded by an aura of constitutional symptoms: weakness, midfrontal headache, pain over the medial canthi of both eyes, dizziness and cold skin. The duration of these hemorrhages varied from several hours to several days. In April, 1951, the patient had the first episode of painless hematuria associated with menstruation, and since then had had several such episodes. The initial hematuria required hospitalization for one week. Extensive studies performed at the School of Tropical Medicine all yielded normal results (serum calcium, cevitamic acid blood level, prothrombin time, bleeding time, coagulation time, platelet count, serologic reaction of the blood, skull x-ray, sinus x-rays, tourniquet tests, sigmoidoscopy).

The patient was not seen from July 9, 1951, until November 16, 1955, when she was admitted to the San Juan City Hospital Out-Patient Department because of recurrent bleeding episodes from the eyes that had persisted in association with the menstrual periods since the onset of her illness. During the interim she had been given cortisone, Adrenosem, vitamin K, vitamin C and thromboplastin, without much benefit. Five months previously she had had a spastic state, with loss of conscious-

ness for 30 minutes, that left no sequela.

On April 27, 1956, while the patient was in the Out-Patient Department for studies, she had a severe episode of bleeding through both eyes. She was in her second day of menstruation. During the next two months she was hospitalized four times in her home town because of severe bleeding from the eyes, ears and nose. On August 20, 1956, she was admitted to the San Juan City Hospital for further studies, and on August 21 (10 days prior to menstruation) the patient had a severe episode of bleeding through the eyes, nose and ears that lasted one day. She then felt well until August 28, 1956, when she developed nervousness, dizziness, a stuffy nose, headaches, nausea, vomiting and mild left upper quadrant pain. On August 31, 1956, she started to bleed through the eyes, ears and nose, and for the first time she bled per rectum. She passed bright red blood with clots. On September 1, 1956, menstruation started and lasted for four days. She continued to bleed intermittently through these sites until September 10, 1956. On September 14, 1956, a sigmoidoscopy failed to reveal any abnormality. After she had been on a knee-chest position for 15 minutes she started to bleed through the eyes. The patient stated that bending over had previously induced episodes of bleeding through the eyes, particularly during the days prior to, during and following menstruation.

Physical examination upon admission to the hospital was essentially negative except for a perforated right eardrum and carious teeth. During the bleeding episodes, examination of the various orifices revealed a generalized oozing of blood from the mucosal surfaces. Ophthalmologic examination using the slit lamp and the binocular microscope revealed marked hyperemia of the tarsal conjunctivae, with marked tortuosity and engorgement of the blood vessels. There was edema of the conjunctivae in both eyes. The deep and superficial small vessels in the lower palpebral conjunctivae showed marked branching and tortuosity. Near the external canthi there were widely dilated and tortuous veins. The vessels in the episclerae and bulbar conjunctivae showed dilatation and tortuosity, but it was less marked than in the palpebral conjunctivae. No bleeding points were seen, and no blood was seen coming from the puncta lacrimalia. Pressure on the lacrimal sacs failed to extrude blood from the puncta lacrimalia. The conjunctivae had a granular appearance. There was oozing of bloody secretion from both conjunctival surfaces.

Laboratory studies on February 17, 1956, revealed the following: hemoglobin, 11.9 gm. (82%); red blood cells, 5,000,000; white blood cells, 10,550, with 62% polymorphonuclears, 14% lymphocytes, 1% monocytes and 23% eosinophils. Color index, 0.8. Urine, normal. *Trichuris trichiura* was reported to have been recovered from the stool. The guaiac test was negative. Platelet count, 178,000/mm.³; coagulation time, two minutes; bleeding time, one minute, 21 seconds; prothrombin time, 15.5 seconds (control, 15.5 seconds).

Laboratory studies on August 21, 1956, revealed the following: sedimentation rate, 18 mm./hr.; clot retraction, completed in three hours; reticulocyte count, 0.7%; prothrombin consumption, 38.5 seconds.

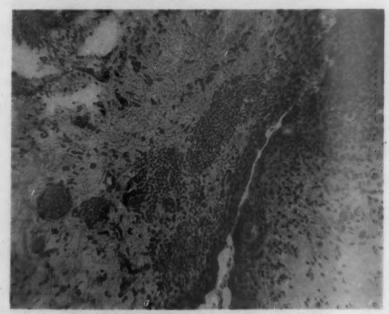


Fig. 1. Inflammatory cells and edema in the subepithelial tissues. Prominent engorgement and telangiectasia with recent hemorrhage. $(80\times)$.

Laboratory studies on September 5, 1956, during a bleeding episode, revealed the following: clot retraction, completed in one hour; prothrombin time, 14 seconds (control, 14 seconds); bleeding time, two minutes; clotting time, five minutes; platelet count, 180,000 (adequate smear); prothrombin consumption, one minute; quantitative fibrinogen, 0.3 gm.%; serum calcium, 9.9 mg.%; cholesterol, 194 mg.%; serum alkaline phosphatase, 1.6 unit; serum phosphorus, 2.9 mg.%; thymol turbidity, 5.3 units; Hanger's test at 24 and at 48 hours, 1 plus.

X-ray studies of the chest and sinuses on August 20, 1956, were reported as negative.

A biopsy of the conjunctiva was done on September 5, 1956, during a bleeding episode (figures 1, 2 and 3). The secretion of mucus was increased. Beneath the epithelial layer there was a narrow zone of moderately dense infiltration with plasma cells, polymorphonuclears and large mononuclear cells. The neutrophils also infiltrated the epithelial layer. The subconjunctival connective tissue was edematous

and showed recent hemorrhage. The blood vessels were markedly congested and dilated.

Diagnosis: Acute and chronic conjunctivitis, hemorrhage into conjunctivae, vascular congestion and telangiectasia.

Treatment: Because the exact etiology of this condition is still unknown, specific measures directed to the correction of this bleeding disorder in our patient had been unsuccessful. During the eight-year period that she had had the condition, attempts to control or prevent bleeding using substances like vitamin C, vitamin K, calcium, Adrenosem, thromboplastin and rutin had failed.

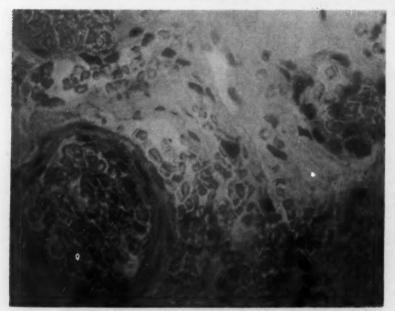


Fig. 2. Congestion and telangiectasia of subconjunctival blood vessels. Edema of the vessel walls with swollen endothelium. Hemorrhage into the edematous subepithelial tissues. $(350 \times)$.

In 1952, Koch, Escher and Lewis ⁹ reported the successful use of estrogen alone or in combination with testosterone in controlling epistaxis in five patients with hereditary hemorrhagic telangiectasia. These authors observed that epistaxis occurred more frequently in this condition about five days prior to menstruation. Because of the close similarity between this disease and the case being reported (i.e., the common occurrence of telangiectasia and periodic bleeding), it was decided to treat our patient with these substances.

On June 22, 1956, one week prior to the onset of menstruation, testosterone propionate, 25 mg. intramuscularly daily for three days, followed by methyltestosterone, 10 mg. three times a day, was started and continued for another week after the end of menstruation. The duration of menstruation was reduced from the usual five to six days to only three days. The menstrual flow was markedly reduced in amount, and bleeding from the orifices did not occur. When testosterone was discontinued the patient had a large hemorrhage through the eyes, ears and nose that lasted about an hour (figure 4). The following month methyltestosterone, 10 mg.

815

three times a day, was again started one week prior to the expected date of menstruation, and was continued for another week afterwards. Bleeding from the orifices was successfully inhibited. On August 20, 1956, the patient was admitted to the San Juan City Hospital for diagnostic studies. During this period medication (testosterone) was withheld. During the period August 21 to September 10, 1956, she had several episodes of bleeding. Menstruation started on September 1, 1956, and ended on September 5, 1956. Since discharge from the hospital the patient has been able to prevent bleeding through the orifices by using methyltestosterone as previously. So far we have not tried estrogens in this patient.

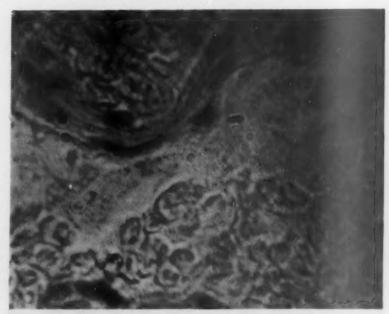


Fig. 3. An oil immersion photomicrograph to show the edema of the wall of the vessels with the swollen and separated endothelial cells. This is highly suggestive of diapedesis. $(800 \times)$.

COMMENT

In 1953 Landesman et al. 10 reported a detailed study of the vascular bed of the bulbar conjunctivae during the menstrual cycle of 15 normal women between the ages of 18 and 36 years. Daily observations using the slit lamp and binocular microscope (magnification 150 ×) revealed:

1. During the menstrual flow (first three days) there were marked reduction in rate of blood flow, scattered segmentation, increased vasomotion, thinning and attenuation. The venules became less full and narrower. Slow blood flow produced a granular appearance. The capillary bed became ischemic with slow blood flow.

2. During the next three to five days of menstrual flow (transitory phase), there was a gradual increase in vascularity and rate of blood flow. Segmentation, granularity, vasomotion and ischemia were reduced.

 From the end of the menses to ovulation (proliferative phase) the blood vessels returned to average caliber, the rate of flow was accelerated, and the capillary bed was normal.

4. During ovulation (24 to 48 hours) there were minimal and inconstant

vascular phenomena.

5. During the secretory phase the arterioles became progressively dilated and filled, with an increase in the rate of blood flow; the venules were engorged and capillaries were filled.



Fig. 4. Face of patient showing congestion and hemorrhage.

6. During the middle of this period the blood flow became slower, with a progressive increase in granularity. The vessels remained dilated and engorged (present in 13 of the 15 women studied).

7. During the one to three days prior to the onset of and including the first two days of menstruation there was a period of arteriolar vasoconstriction and reduced blood flow in all vessels. The arterioles became attenuated, and vasomotion became characteristically at a maximum. There was marked ischemia.

Similar gross and microscopic vascular changes were noticed in our patient during the menstrual cycle. Bleeding occurred during the period of maximal congestion and dilatation of blood vessels through a process of extravasation of blood or diapedesis, since it was impossible to discover any bleeding points from any of the mucosal surfaces in the conjunctivae, nasal orifices, ears or rec-

tum on repeated examinations. Increasing the venous pressure in the head, either by tilting the patient with her head down or by applying a tourniquet around the neck, would induce an episode of bleeding through the conjunctivae during the period of maximal vascular congestion. This observation suggests that in our patient there is an increase in vascular fragility during this particular

period of the menstrual cycle.

The cyclic mechanism responsible for these vascular changes appears to be hormonal in nature and probably identical to those occurring in the endometrium during the menstrual cycle. The pituitary gland through its gonadotropic hormone is directly responsible for the changes in the ovaries that, in turn, control the cyclic changes in the endometrium, the follicle-stimulating hormone being responsible for the development of the follicle and the luteinizing hormone for the development of the corpus luteum. Soon after the end of menstruation there is a gradual increase in urinary gonadotropins (follicle-stimulating hormone), with a peak secretion at about five to seven days prior to menstruation. As the follicle develops under the influence of the follicle-stimulating hormone the urinary estrogens gradually increase to a maximum, and if ovulation occurs, the corpus luteum hormone is also secreted, to reach a peak at about one to three days prior to the onset of menstruation. By this time the high titers of these ovarian hormones have inhibited the pituitary gland from secreting gonadotropic hormone. As a result of this inhibition of pituitary gonadotropin there is a release of stimulus on the ovary and a sudden drop in estrogens and progesterone secretion. This sudden drop of the ovarian hormones is the precipitating mechanism for the onset of menstruation, and in our patient it was the probable cause of her vicarious bleeding.

Because testosterone is known to inhibit the pituitary gland and to produce atrophy of the endometrium, it seemed reasonable to start this medication one week prior to the onset of menstruation to obtain an early inhibition of the gonadotropic stimulus of the pituitary gland on the ovary and thus prevent a sudden drop in the estrogen and progesterone secretion. As a result of its use, the duration of menstruation was reduced from the usual four to five days to only three days, and the amount of menstrual flow was markedly diminished. Bleeding from the orifices prior to or during menstruation has been inhibited during the last two menstrual cycles. Medication has been continued for another week after the end of menstruation to prevent a delayed or rebound stimulus of the pituitary gland on the ovary, since stopping medication too prematurely (on the last day of menstruation) resulted in a severe episode of bleeding. A similar inhibitory influence has been observed by Koch, Escher and Lewis 9 in preventing the periodic epistaxis in five patients with hereditary hemorrhagic telangiectasia by the use of estrogen alone or in combination with testosterone. As in our patient, sudden withdrawal of medication resulted in severe epistaxis in one patient. Daily hormone therapy for 14 months in this series of patients resulted in adequate control of bleeding.

SUMMARY AND CONCLUSIONS

1. A unique case of vicarious bleeding from the eyes, nose, ears, urethra and rectum occurring in association with menstruation has been reported and the literature on this subject reviewed.

The possible mechanism responsible for the cyclic bleeding in this condition is discussed.

3. The use of testosterone in the usual dosage appeared to inhibit the onset of bleeding in this patient when started one week prior to the onset of menstruation and continued for another week after the cessation of menstrual flow. Sudden withdrawal of medication at the end of menstruation should be avoided to prevent recurrence of bleeding.

ACKNOWLEDGMENTS

I am indebted to Dr. Guillermo Picó, Professor of Ophthalmology of the University of Puerto Rico School of Medicine, for examining this patient and obtaining the biopsy from the conjunctiva, and also to Dr. Enrique Koppisch, Professor of Pathology, and Dr. Raúl Marcial Rojas, Assistant Professor of Pathology of the University of Puerto Rico School of Medicine, for the microscopic study of the biopsy material, and to Dr. Mercedes V. Torregrosa, Chief of the Central Laboratory of the San Juan City Hospital, for the extensive survey of the clotting mechanism in this patient.

SUMMARIO IN INTERLINGUA

Sanguination extragenital via le orificios de oculos, aures, naso, recto, e urethra in association con le menstruation es un condition rar. Ben que plure reportos de menstruation substitutive via plures del orificios mentionate se trova in le litteratura del passate 70 annos, nulle caso de sanguination simultanee via oculos, naso, aures, recto, e urethra in association con le menstruation ha unquam essite publicate. A causa del exceptionalitate de iste condition, le presente caso es describite.

Le patiente, un femina maritate de racia blanc de 30 annos de etate, habeva habite episodios de sanguination extragenital via le supra-mentionate orificios in association con su menstruationes durante le passate octo annos. Le examine physic durante un episodio de sanguination revelava un exsudation generalisate de sanguine, que habeva le olentia characteristic del fluxo menstrual, ab le superficies mucosal del orificios in question.

Le examine del conjunctivas durante un episodio de sanguination, per medio del lampa a fissura e del microscopio binocular, revelava marcate grados de hyperemia del conjunctivas tarsal e forte tortuositate e congestion del vasos de sanguine. Edema conjunctival se trovava in ambe oculos. Le micre vasos, profunde e superficial, in le conjunctivas infero-palpebral monstrava forte branchification e tortuositate. Iste vasos, specialmente le venas, esseva apparentemente multo dilatate. Nulle punctos de sanguination esseva notate, e nulle sanguine exiva visibilemente ab le punctos lacrimal. Pression applicate al saccos lacrimal non resultava in le extrusion de sanguine ab le punctos lacrimal. Le apparentia del conjunctivas esseva granular, e un secretion sanguinose exsudava ab le superficies conjunctival de ambe oculos e etiam ab le nares e aures.

Extense studios laboratorial del mechanismos coagulatori esseva normal tanto ante como etiam durante le episodios de sanguination. Le test del fragilitate capillar esseva normal. Un biopsia ab le conjunctivas durante un episodio de sanguination revelava un augmento del secretion de muco e un moderatemente dense infiltration per cellulas plasmatic, polymorphonucleares, e grande mononucleares. Le histos conjunctive sub le conjunctivas esseva edematose e indicava hemorrhagias recente. Le vasos de sanguine esseva marcatemente congestionate e telangiectatic.

Iste periodic episodios de sanguination es probabilement causate per le mesme mechanismo vasculo-hormonal que age in le utero, i.e. le alterationes vascular resulta ab le activitate hormonal del axe pituitari-ovarian.

Substantias como vitamina C, vitamina K, cortisona, calcium, Adrenosem, thromboplastina, e rutina esseva sin beneficio pro nostre patiente. Propionato de testoste-

rona, sequite per methyltestosterona in le doses usual, ha inhibite le episodios de sanguination in iste patiente, apparentemente per le inhibition precoce del glandula pituitari, resultante in un reducite secretion de hormon folliculo-stimulante e consequentemente un reducite secretion de estrogeno e progesterona per le ovarios. Quando iste nivellos hórmonal es reducite, un abassamento precipite del nivellos de estrogeno e progesterona es prevenite, e isto inhibi le sanguination anormal in nostre patiente. Il es probabile que castration resultarea in un curation permanente.

BIBLIOGRAPHY

- 1. Duncan, J. M.: London Medical Times, Feb., 1884.
- 2. Claiborne, H. J.: A case of vicarious menstruation from the lower lids, J. A. M. A. 39: 631 (Sept. 13) 1902.
- 3. Condit, W. H.: Compensatory or vicarious menstruation, Am. J. Obst. and Gynec. 73: 238-251, 1916,
- 4. Roth, O. H.: Monatschr. f. Geburtsh. u. Gynäk. 51: 41, 1920.
- 5. Kieser, K.: Clin. ostet. 35: 593, 1933.
- 6. Saitz, O.: Abstr., Ber. ü. d. ges. Gynäk. u. Geburtsh. 30: 557, 1935.
- 7. Frank, R. T.: The female sex hormones, 1929, Charles C Thomas, Springfield, Illinois,
- 8. Wolff, H. G.: Headache and other head pains, 1948, Oxford University Press, New York, pp. 260-261.
- 9. Koch, H. J., Escher, G. C., and Lewis, J. S.: Hormonal management of hereditary hemorrhagic telangiectasia, J. A. M. A. 149: 1376 (Aug. 9) 1952.
- 10. Landesman, R., Douglas, R. G., Dreishpoon, G., and Holze, E.: The vascular bed of the bulbar conjunctiva in the normal menstrual cycle, Am. J. Obst. and Gynec. 66: 988 (Nov.) 1953.

STAPHYLOCOCCAL SEPTICEMIA WITH RECURRENT SPONTANEOUS PNEUMOTHORAX *

By Albert Schweich, M.D., and Joseph Fierstein, M.D., New York, N. Y.

THE incidence of staphylococcal infections appears to be rising, 1, 2, 3 particularly in hospital populations. This is probably due to antibiotic-resistant organisms and cross infection.3, 4, 5 Although statistics of incidence and mortality are difficult to evaluate and require further investigation, antibiotic resistance of the staphylococcus has been clearly demonstrated after each new antibacterial agent has come into common use.3,6 Clinical surveys indicate that the mortality rate of generalized infections was reduced from over 80% to 28% following the introduction of penicillin, rose subsequently to 54%, and at present is as high as in the pre-antibiotic era.4

The complications of generalized staphylococcus infections are widespread and continue to pose serious problems for the clinician in his management of a given case.

The following case of staphylococcal septicemia is reported because it dem-

* Received for publication July 24, 1957.
From the Medical Services, Montefiore Hospital, New York, N. Y.
Requests for reprints should be addressed to Albert Schweich, M.D., 115 West 238th Street, New York 63, N. Y.

onstrates a number of clinically significant features, particularly the development of recurring, spontaneous pneumothorax.

CASE REPORT

A 14 year old Irish male was admitted to Montefiore Hospital on October 2, 1956, with fever, cough, abdominal pain, nausea, vomiting and diarrhea. In early childhood he had had measles and pertussis. For the last nine years an unchanging,

TABLE 1 Laboratory Data

| | Hospital Day | | | | | |
|---|----------------------------------|----------|---------------------------------|------------|-----------|-------------------------|
| | Admission | 3rd | 6th | 8th | 12th | Prior to Discharge |
| Blood Counts: White blood cells Polymorphonuclear | 7,800/cu. mm. | 18,000 | 11,000 | | | 5,700 |
| leukocytes | 75 | 73 | 66 | 1 | | 45 |
| Non segmented | 13 | 14 | 5 | | | 3 |
| Lymphocytes | 6 | 7 | 16 | | | 36 |
| Metamyelocytes | 2 | 3 | 4 | | | 1 |
| Basophils | 1 | | 1 | 100 | | 3 |
| Atypical lymphocytes Eosinophils | 3 | 1 | 4% | | | 7% |
| Monocytes | and | 1 | 36.01 | | 1 | 41% |
| Hematocrit Erythrocyte sedimenta- tion rate | 39% 85 mm./hr. | | 36% | - | | 41% |
| Jrinalysis: | 00 mm./ m. | | | 1 | | |
| Specific gravity | 1.016 | 1.010 | 1.018 | 1.010 | 1.010 | 1.010 |
| Albumin | Trace | 0 | 1 plus | Trace | Trace | 0 |
| RBC/HPF | 3-10 | 0 | 4-10 | 1-5 | 0-1 | 0-1 |
| WBC/HPF | 0-3 | Many | 3-6 | 0-1 | 0 | 0 |
| Bacteria | Positive | 24,441,3 | | | | |
| WBC casts | 1 odierec | Many | | | | |
| Jrine Culture | | SVERENS | Negative | | 1 - 1 | |
| Bacteriology: | | | receative | | | |
| Blood cultures | 4-positive for | Negative | | Negative | Negative | 1000 |
| Diood cultures | coagulase-posi- | Memerie | | . ACBMCIVC | . remaine | |
| | tive hemolytic Staphylococcus | | | - 400 | | |
| | aurens | | | 0.116 | | |
| Throat Culture . | Coliform bacilli | | | Coliform | | |
| | | | | bacilli | 1 | |
| Sputum Culture: Stool smear and culture | | | Escherichia coli and pseudo- | | | |
| | | | monas. No enteric patho- | | | |
| Blood Chemistry: | | | E-110 | | | |
| Alkaline phosphatase | 14.9 Bodansky units | | 7.9 Bodansky units | | | 4.5 Bodan- sky units |
| Cephalin flocculation | 4 plus | | 4 plus | | | 3 plus |
| Thymol turbidity | 5 units | | | | | |

Bilirubin, fasting blood sugar, blood urea nitrogen, sodium, potassium, chlorides, carbon dioxide combining power, heterophil antibody test, cold agglutinins, enteric agglutinins, and lupus erythematosus preparations were all negative or normal. The electrocardiogram was consistently normal. First and second strength purified protein derivative skin tests for tuberculosis were negative.

loud systolic murmur which had the characteristics of an interventricular septal defect had been observed. At age five, he had had occasional pain in his left heel, but there was no history of rheumatic fever or of any cardiovascular symptoms.

The present illness had begun one week prior to admission with fever, sore throat, headache and vomiting. Three days before admission the only positive physical findings were fever, an intensely red pharynx and several small, nontender, posterior cervical lymph nodes. The patient received oral penicillin and Achromycin for two days. The pharyngitis improved but the fever persisted, with daily rises to 104° F.

Vomiting persisted, and upper abdominal pain and diarrhea subsequently developed. A macular skin eruption appeared on the arms and spread to the abdomen and thighs. At this time the patient developed a productive cough.

Physical Examination: On admission this boy was acutely ill, lethargic and markedly dehydrated, but not cyanotic or dyspneic. He had a cough and was expectorating blood-streaked sputum. His temperature was 104.2° F.; pulse, 112 and

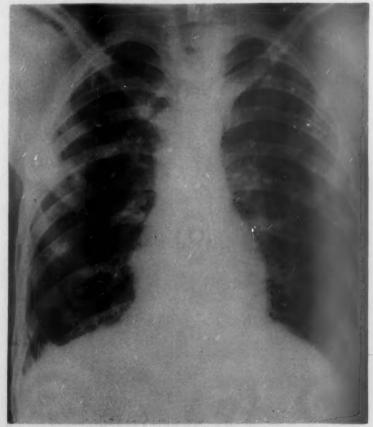


Fig. 1. Third hospital day roentgenogram, showing increased nodular densities in both lungs.

regular; respiration, 30 per minute; blood pressure, 110/70 mm. of Hg. His face was flushed. There was a diffuse, macular, erythematous eruption over the chest, axillae, both hips and the dorsum of both hands. The pharynx was moderately injected; the tongue was dry. There were no cutaneous or mucosal petechiae. Small posterior cervical and axillary nodes were palpable. The lungs showed normal resonance on percussion. There were no râles on auscultation, but an occasional expiratory wheeze was heard in the right and left midlung fields posteriorly. Heart: a harsh grade III systolic murmur, slightly more prominent than in the past, was

heard over the entire precordium but was loudest in the third left intercostal space just to the left of the sternum. P_2 was louder than A_2 . The point of maximal intensity was palpable at the fifth left intercostal space within the midclavicular line. There was no rub, thrill or gallop.

The abdomen was soft, with slight guarding, mild pain and tenderness in the right upper quadrant. The liver, spleen and kidneys were not palpable. Rectal

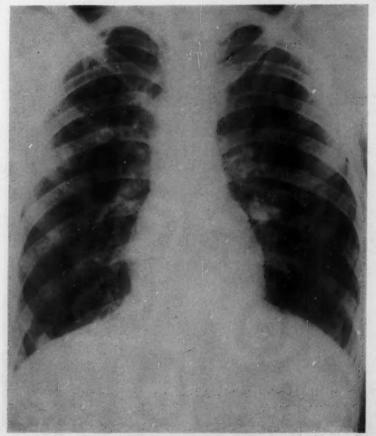


Fig. 2. Ninth hospital day roentgenogram, illustrating thin-walled annular shadows throughout both upper lung fields.

examination was normal. There were mild pain and tenderness in the left heel, but no joint pain, swelling or tenderness. A small hematoma was noted under a callus on the sole of the right foot. Neurologic examination was normal.

Laboratory Data: For summary of laboratory data, see table 1.

Course in Hospital: On admission the patient appeared to be quite toxic, and after four blood cultures were obtained he was given intravenous fluids with vitamins and started on Chloromycetin, 250 mg. intramuscularly every six hours. Twelve hours later, Staphylococcus aureus was cultured from the blood. The organism was

resistant to penicillin, 2 plus sensitive* to streptomycin, neomycin, Albamycin, erythromycin, Terramycin, bacitracin, Aureomycin and Furadantin, and 1 plus sensitive to Chloromycetin. The patient was then given 20,000,000 units of aqueous penicillin intravenously per day, plus 2 gm. of streptomycin and 2 gm. of erythromycin per day. Chloromycetin was discontinued. In the subsequent three days the patient showed marked clinical improvement, with a rapid drop in temperature to 98.6° F.

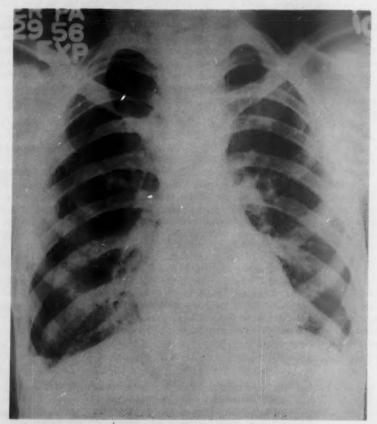


Fig. 3. Roentgenogram on nineteenth hospital day, showing right-sided pneumothorax with prominent subpleural radiolucency.

and disappearance of the rash. He continued, however, to complain of pain in the right upper quadrant. Examination revealed tenderness in both upper abdominal quadrants without muscle guarding or rebound tenderness. Urinalysis showed pyuria (table 1). On the sixth hospital day the temperature rose again, and examination now revealed mild bilateral tenderness in the costovertebral angle. Novobiocin, 500 mg. every six hours by mouth, was added to the therapeutic régime, and fever, abdominal pain and pyuria subsided.

^{*}Two plus represents maximal sensitivity according to the disc method of sensitivity studies used in this hospital.

X-rays of the chest during the initial period showed increasing bilateral nodular densities (figure 1) which were interpreted as consistent with septic emboli or multiple pulmonary infarcts. Abdominal films revealed mild inhibition ileus but no hepatosplenomegaly or renal calculi. Cough and hemoptysis subsided gradually, but on the ninth hospital day the patient again had fever of 103.6° F, with no significant changes in his clinical status. X-rays of the chest now showed the development of multiple radiolucent areas, about 1 cm, in diameter, scattered throughout both upper lung fields (figure 2). The patient again complained of mild pain in the right upper quadrant and was slightly tender in this region. The cephalin flocculation reaction was 4 plus, as on admission; whereas alkaline phosphatase had decreased from 14.9 to 7.9 Bodansky units. The blood count showed a slight eosinophilia. At this time the possibility of penicillin sensitivity as a causal factor for fever and eosinophilia was considered, penicillin was discontinued, and Terramycin, 400 mg, intramuscularly daily, was added. The patient became afebrile. X-rays of the chest showed some resolution of the pulmonary densities. There was no significant change in the character of the systolic murmur described, and no petechiae appeared.

On the nineteenth hospital day the patient complained of sharp pain in the right anterior portion of the chest, accentuated by cough, respiration and motion. Physical examination was not revealing, but an x-ray of the chest demonstrated a right-sided pneumothorax with 20% collapse of the lung (figure 3). Temperature at this time was 99° F. On conservative therapy no untoward sequelae were noted, and the right lung reexpanded in three days. The patient had no complaints and was doing well. On the twenty-sixth hospital day he again complained of transient right anterior thoracic pain, not accompanied by dyspnea, cyanosis or temperature elevation. Examination revealed slightly diminished breath sounds over the right upper portion of the chest posteriorly and in the right axilla, with hyperresonance to percussion. X-rays of the chest now revealed recurrence of the right-sided pneumothorax, with a small amount of pleural effusion at the right base. The patient again responded well to conservative management, and steadily improved until time of discharge.

The patient developed a monilia infection of the mouth and pharynx which responded favorably to 1% gentian violet and mycostatin. For one week prior to discharge the patient was entirely without antibiotics, was ambulatory and had no complaints. Subsequent observation at home showed an uneventful convalescence, with gain in weight, no subjective complaints, no abnormal signs and a normal x-ray of the chest, and blood count.

DISCUSSION

We believe that four aspects of this case require emphasis: first, the difficulty of diagnosis before blood cultures are reported; second, the question of origin of the staphylococcal infection; third, the successful use of a combination of antibiotics, although without clear knowledge which of these was decisive in the cure; and finally, the development of pneumothorax in the course of pulmonary lesions.

The history of this boy gave no certain clue to the diagnosis. On admission to the hospital the diagnosis was fever of unknown etiology. The observation of an intensely red throat with response to penicillin and the pain in one heel suggested rheumatic fever, but there was no articular swelling, redness or heat, and no leukocytosis. Infectious mononucleosis was considered in view of the enlarged cervical and axillary nodes, tenderness in the liver area and a skin rash, but the findings in the peripheral blood were not compatible with this diagnosis. Enteric fever, penicillin reaction and a modified form of a childhood exanthem

were possibilities, but no confirmatory data were available, and the subsequent course of the illness was against these clinical diagnoses.

The most probable diagnosis appeared to be bacterial endocarditis. In the presence of a previous cardiac murmur and a positive blood culture, and in spite of the absence of leukocytosis, petechiae, splenic enlargement and even with a relatively benign course, bacterial endocarditis remains a distinct possibility.^{7, 8, 10} However, as Fisher and associates ¹⁰ state, it is conceivable that bacteremia may exist in patients with heart disease without involvement of the endocardium.

Blood cultures, x-rays of the chest, urinalysis and liver function tests established the diagnosis of a S. aureus bacteremia with foci in the lungs, kidneys and liver.

The portal of entry of this infection remains uncertain. The pharynx would appear to be the most likely site. A penicillin-resistant strain of staphylococcus may have been introduced into the patient's home by his sister who, as a student nurse, is in daily contact with ward patients. There is much evidence that nasal and fecal carriers among hospital personnel are an important reservoir of anti-biotic-resistant staphylococci. 11, 12, 18 The skin is the second possible source of infection, with a plantar callus traumatized with a razor blade some weeks and again some days before the onset of the illness. Neuhof and Berck, 14 in a series of 373 patients with staphylococcal empyema, found that 22.5% of 182 children and 45.5% of 191 adults had an active or subsiding skin infection as the chief site of entry. Skinner and Keefer 15 found the skin to be the primary focus in 40% of cases of staphylococcus bacteremia.

The therapeutic armamentarium employed in this case requires explanation. Initially, an intravenous infusion with 20,000,000 units of penicillin per day in combination with streptomycin and erythromycin was administered, and later, novobiocin was added. When the studies showed no sensitivity of the organism to penicillin, it was continued because of recent evidence that no real correlation exists between lack of sensitivity in vitro, especially by the disc method, and the activity in vivo of very large doses. Fisher and his associates ¹⁰ feel that "regardless of laboratory findings, the therapeutic régime should include massive doses of penicillin." Rogers ¹⁶ agrees with this view, and mentions that laboratory studies show that most staphylococcal strains are not homogeneous in their susceptibility to antibiotics. Penicillin, then, might suppress most of a bacterial population, although sensitivity studies would not indicate it.

The addition of other antibiotics will obscure judgment as to which agent was decisively effective, but when one is dealing with staphylococcal septicemia there is no choice but to use combinations of drugs which may be additive and synergistic.

In our case the blood cultures became negative on the second day of treatment. The lowered but continued elevations of temperature and the rise in the leukocyte count were thought to be due to focal lesions in lungs, kidneys and liver, not accessible to antibiotics. The possibility of drug fever could not be completely ruled out in view of a mild eosinophilia. Urinalysis became normal and cephalin flocculation reaction decreased slowly. The pulmonary densities developed into annular radiolucent shadows, and finally pneumothorax developed.

Pneumothorax in the course of pulmonary infection has been reported in infancy, 17, 18, 19, 20 less frequently in older children, and rarely in adults. 21, 22

It is believed that pneumothorax may be the result of either necrotizing pulmonary lesions or the development of postinfectious pneumatoceles or subpleural The first of these mechanisms was described by Neuhof and Berck 14 as "carbuncles of the lung," rupturing into the pleural cavity. X-rays of the chest showed fluid and air in the pleural space, and often circular areas of rarefaction or of increased density adjacent to the pleural surface, representing drained or undrained abscesses. They felt that these radiologic features were pathognomonic of staphylococcal pulmonary infections. Similar features of staphylococcal pneumonia were reported by Forbes 28 in 1946. The second possible sequence of events is the formation and rupture of subpleural blebs or pneumatoceles. Subpleural blebs are formed by the rupture of alveoli and dissection of air between pulmonary parenchyma and visceral pleura. Pneumatoceles are "non-epithelialized positive pressure cavities produced by hyperinflation of a parenchymal defect from infection." 24 Such postinfectious air spaces were described in the German literature by Duken 25 in 1927 and Zarfl 26 in 1932. Kanof and associates 27 mention the formation of subpleural blebs in staphylococcal lung infections. Glazenburg,28 in cases of staphylococcal sepsis, reported multiple infiltrations and cystlike cavities which occasionally were transformed from one into the other. Lindskog 29 and Stickler and associates 30 consider a check-valve mechanism in the formation of such air cysts. In a discussion of cavities developing in infants and children during infections of the respiratory tract, Caffey 31 also postulates hyperinflation of a pulmonary segment, but states that necrosis of lung tissue cannot be excluded as a partial

The x-rays of the chest in our case show multiple nodular densities changing into air-containing spaces, one of which is seen adjacent to the pleural surface of the right upper lobe (figure 3). These radiolucent areas may represent either of the pathologic processes mentioned. If, as we believe, they were abscess cavities, the development of empyema may have been prevented by the antibiotic therapy.

SUMMARY

1. A case of staphylococcus septicemia with pulmonary, renal and hepatic involvement is reported.

2. A cure was achieved with a combination of antibiotics, including massive doses of penicillin, in spite of absence of in vitro sensitivity to this antibiotic.

A prominent finding was the development of recurrent episodes of spontaneous pneumothorax.

ACKNOWLEDGMENT

The authors wish to thank Dr. Harold Rifkin for his invaluable assistance in the management of this case and in the preparation of this paper.

SUMMARIO IN INTERLINGUA

Es reportate un caso de septicemia staphylococcal con affection de pulmon, ren, e hepate e disveloppamento tardive de recurrente pneumothorace spontanee.

Il se tracta de un puero de 14 annos de etate, admittite al Hospital Montefiore con febre, tusse, sputo sanguinee, nausea, vomito, diarrhea, e un macular eruption cutanee. Iste symptomas se habeva disveloppate post un septimana de pharyngitis

827

febril. Un murmure cardiac, compatibile con defecto del septo interventricular habeva essite notate depost le prime infantia.

Al tempore del hospitalisation, le diagnoses prendite in consideration includeva febre rheumatic, mononucleosis infectiose, febre enteric, reaction penicillinic, exanthema de infantia, e endocarditis bacterial. Culturas de sanguine, roentgenogrammas thoracic, tests del function hepatic, e urinalyses establiva le diagnose de septicemia per *Staphylococcus aureus* con affection del pulmones, del renes, e del hepate. Le possibilitate de endocarditis staphylococcal non poteva esser excludite.

Le porta de invasion de iste infection esseva forsan le pharynge e forsan le pelle. Le transmission de un infection per staphylococcos penicillino-resistente per un studente-infirmera, qui esseva un membro del familia, esseva un possibilitate.

Ben que le organismo se monstrava resistente contra penicillina in un test per le methodo a discos, massive doses intravenose de penicillina esseva administrate in supplementation del therapia a streptomycina, erythromycina, e novobiocina. Iste combination resultava in le curation del patiente. Ben que nos non pote determinar le qual del antibioticos esseva de importantia decisive, il se trova in le litteratura reportos de recente observationes del non-correlation inter le sensibilitate in vitro de specific organismos e le activitate in vivo de massive doses de penicillina.

Densitates nodular in le roentgenogramma thoracic se disveloppava in translucentias anular. Un de istos esseva situate in le vicinitate del superficie pleural del lobo dextero-superior. Pneumothorace dextere se disveloppava le dece-none die e recurreva le vinti-sexte die del hospitalisation. Pneumothorace in le curso de infection pulmonar occurre como resultato de lesiones necrotisante, de pneumatoceles postinfectiose, o de vesiculas subpleural. In le presente caso, pneumothorace se disveloppava probabilemente como resultato de un ruptura de un cavitate de abscesso pulmonar, e empyema esseva prevenite per le therapia antibiotic.

BIBLIOGRAPHY

- Prissick, F. H.: Antibiotic-resistant staphylococci and related infections, Am. J. M. Sc. 225: 299, 1953.
- Howe, G. W.: Postoperative wound infections due to Staphylococcus aureus, New England J. Med. 251: 411, 1954.
- Finland, M.: Antibiotic-resistant micrococcic infections, guest editorial, J. A. M. A. 158: 188, 1955.
- Spink, W. W.: The clinical problem of antimicrobial-resistant staphylococci, Conference on staphylococcal infections, Ann. New York Acad. Sc. 65: 175, 1956.
- Spink, W. W.: Staphylococcal infections and the problem of antibiotic-resistant staphylococci, Arch. Int. Med. 94: 167, 1954.
- Clough, P. W.: Resistance of micrococci to antibiotics, editorial, Ann. Int. Med. 42: 954, 1955.
- Dowling, H. F., Lepper, M. H., Caldwell, E. R., and Spies, H. W.: Staphylococcic endocarditis: analysis of 25 cases treated with antibiotics, together with review of recent literature, Medicine 31: 155, 1952.
- Fleming, H. A., and Seal, R. M. E.: Staphylococcus infection following cardiac surgery, Thorax 10: 327, 1955.
- Dalton, J. C., Williams, B., and Atkins, L.: Staphylococcal endocarditis after mitral valvulotomy, New England J. Med. 254: 205, 1956.
- Fisher, A. M., Wagner, H. N., Jr., and Ross, R. S.: Staphylococcal endocarditis: some clinical and therapeutic observation on 38 cases, Arch. Int. Med. 95: 427, 1955.
- Barber, M., and Rozwadowska-Dowzenko, M.: Infection by penicillin-resistant staphylococci, Lancet 2: 641, 1948.

- Rountree, P. M., and Barbour, R. G. H.: Nasal carrier rates of Staphylococcus pyogenes in hospital nurses, J. Path. and Bact. 63: 313, 1951.
- Clarke, S. K. R., Dalgleiser, P. G., and Gillespie, W. H.: Hospital cross-infection with staphylococci resistant to several antibiotics, Lancet 1: 1132, 1952.
- Neuhof, H., and Berck, M.: Staphylococcic empyema and pyopneumothorax, Arch. Surg. 30: 543, 1935.
- Skinner, D., and Keefer, C. S.: Significance of bacteremia caused by Staphylococcus aureus: a study of 122 cases and a review of the literature concerned with experimental infection in animals, Arch. Int. Med. 68: 870, 1941.
- Rogers, D. E.: The current problem of staphylococcal infections, Ann. Int. Med. 45: 748, 1956.
- 17. Anderson, W. W., and Cathcart, D. I.: Pneumothorax complicating lobar pneumonia in a four year old boy, Arch. Pediat. 51: 605, 1934.
- Gepp, D.: A case of spontaneous pneumothorax following lobar pneumonia in a child under two years, M. J. Australia 1: 135, 1937.
- Heber, J.: Pneumatocele occurring during pneumonia and rupturing to form pneumothorax, Proc. Roy. Soc. Med. 40: 534, 1947.
- Bass, H. E., Diamond, N., and Schuman, M.: Triad of pneumonia, pneumatocele and spontaneous pneumothorax in infants, J. A. M. A. 154: 143, 1954.
- Thomas, I.: Spontaneous pneumothorax in pneumonia; report of cases, M. Bull. Vet. Admin. 18: 20, 1942.
- Love, L., and King, J. C.: Spontaneous pneumothorax complicating pneumonia, Ann. Int. Med. 40: 153, 1954.
- 23. Forbes, G. B.: Diagnosis and management of severe infections in infants and children; a review of experiences since the introduction of sulfonamide therapy. V. Staphylococcal empyema; the importance of pyopneumothorax as a complication, J. Pediat. 29: 45, 1946.
- Woods, F. M., and Overholt, R. H., in Non-tuberculous diseases of the chest, A. L. Banyai, Editor, 1954, Charles C Thomas, Springfield, Illinois, p. 813.
- Duken, J.: Eine Hals-Lungen Pneumatocele auf der Grundlage eines Abscesses bei einem Saeugling, Ztschr. f. Kinderh. 43: 346, 1927.
- Zarfl, M.: Zur Kenntnis der geschwulstfoermigen Luftansammlungen im Brustraum. Ztschr. f. Kinderh. 54: 92, 1932-3.
- Kanof, A., Epstein, B., Kramer, B., and Mauss, I.: Staphylococcal pneumonia and empyema, Pediatrics 2: 385, 1953.
- Glazenburg, J.: Holtervorming in de long na staphylococcus sepsis, Nederl. tijdschr. v. geneesk. 95: 3388, 1951.
- Lindskog, G. E., and Van Allen, C. M.: Aerodynamics of bronchial obstruction, Arch. Surg. 24: 204, 1932.
- Stickler, G. B., Ellis, F. H., and Mills, S. D.: Lobectomy for suppurative micrococcal pneumonia with pyopneumothorax in an infant, Proc. Staff Meet., Mayo Clin. 30: 276, 1955.
- Caffey, J.: Regional obstructive pulmonary emphysema in infants and children, Am. J. Dis. Child. 60: 586, 1940.

EDITORIAL

NOLLE NOCERE

THE RESPONSIBILITY OF THE PHARMACEUTICAL INDUSTRY *

Nolle Nocere, primum nolle nocere: the first principle of therapeutics. "Do no harm"—literally, "To be unwilling to do harm." This is the principle on which rests public confidence in the physician.

This first principle has stood firm throughout the centuries; only the connotation has changed. But this change, largely the result of the many outstanding advances in pharmacology which we have seen in our time, has been so great as to nearly obscure the principle. The lines of Pope, "Be not the first by whom the new are tried, nor yet the last to lay the old aside," are still sound advice for the practicing physician: but the timing with some has changed to "Better hurry up to use the new drug before it is replaced by a still better one." Or, in a hypercritical mood, "Better hurry up to use the new drug while it is still thought to be effective." As Dr. Harry Dowling 1 pointed out recently, the United States Pharmacopeia added 742 new drugs in the 20 years from 1935 to 1955, four times as many as the

In our mid-twentieth-century world of today, the availability of active drugs with specific therapeutic action enables the physician to cure many diseases promptly and relieve symptoms more effectively. This fact, coupled with his increased understanding of disease, enables him to deal more readily with the emotional, social, and economic aspects of illness. Today physicians are less dependent upon faith and good hygiene and the polypharmacy of our fathers.

182 introduced in the previous two decades from 1915 to 1935.

The fruits of basic biological and chemical studies made over the last 100 years are ripening in our time. In the 1920's, insulin and liver extract appeared. Then there was type-specific antipneumococcus serum for pneumonia, followed by sulfonamides and later penicillin. Subsequently came the broad and narrow-spectrum antibiotics, and more recently the adrenocortical steroids and other drugs.

Drugs with specific therapeutic action require specific and accurate diagnoses. Untoward or toxic side effects are implicit in the action of such active pharmacologic agents.2 The medical profession accepts the appearance of such side effects in a small percentage of patients as the price of obtaining striking therapeutic results in a great many cases. Ponder for a moment

^{*}From a Morning Lecture presented at the Thirty-ninth Annual Session of The American College of Physicians, Atlantic City, New Jersey, April 30, 1958, by George E. Farrar, Jr., M.D., F.A.C.P., Associate Professor of Medicine, Temple University School of Medicine; Medical Director, Wyeth Laboratories, Philadelphia, Pennsylvania.

¹ Dowling, H. F.: Twixt the cup and the lip, J. A. M. A. 165: 657 (Oct. 12) 1957.

² Sollman, T.: Manual of pharmacology, 7th Ed., 1948, W. B. Saunders Company, Philadelphia.

delphia, p. 3.

the untoward effects of, say, cortisone—or chlorpromazine, or chloramphenicol. Each of these agents has marked pharmacologic actions and specific therapeutic applications. In fact, cortisone and chlorpromazine control symptoms and the progress of disorders which cannot be alleviated otherwise. And chloramphenicol, despite rare bone marrow depression, is the only chemotherapeutic agent effective against certain bacterial infections.

Some of you will recall the recognition during the early 1930's that the use of aminopyrine was associated with agranulocytosis. At that time there was no effective antibacterial chemotherapy and blood banks did not exist. Hence, the therapeutic use of aminopyrine was practically discontinued in the United States, though not abroad. By contrast, the agranulocytosis rarely associated with the sulfonamide drugs was a less serious condition. With the availability of active antibiotic drugs and blood transfusions, agranulocytosis-though still a serious and most undesirable entity-has a much more favorable prognosis. In fact, phenylbutazone and subsequently the phenothiazine tranquilizer drugs have found wide clinical application despite the small but potential hazard of agranulocytosis. For that matter, even penicillin may cause severe allergic reactions, even anaphylactic fatal-This does not mean that we have abandoned nolle nocere. Rather, in inducing specific therapeutic effects, we must watch for early signs of known side effects in order to withdraw the drug before severe harm is done or to take immediate steps to neutralize the undesirable manifestations.

All of which leads to the question of the responsibility of the pharmaceutical industry, to both the medical profession and the public.

As the arsenal of medicine, the industry makes weapons against disease readily available to the practicing physician. In so doing, it follows these important procedures: (a) development of useful drugs, in collaboration with university and government scientists and clinicians; (b) production of effective products by qualified chemists, microbiologists and pharmacists; (c) quality control of these products to assure dependability; (d) distribution to practicing physicians in all parts of the world, and (e) equitable pricing.

In the conduct of its daily business, the pharmaceutical industry as a whole lives up to its responsibility in upholding the principle of nolle nocere. Contrary to the statements of some of our medical colleagues who make headlines by denouncing the industry, it is not constituted of a group of opportunists trying to fool the physician and rob the public. The high cost of issuing a new product today means that the responsible physicians and clinical investigators believe on good evidence that a new product warrants wide use. Others may not agree, and the pharmaceutical companies certainly do not claim to be infallible, but the failures are infrequent. A company which loses the confidence of its customers, the physicians, will not stay long in business—any more than the physician whose patients lose confidence in his integrity, his ability, or his interest in them. There is a close parallel!

The pharmaceutical industry functions as the munitions maker of the medical field. It must maintain economical production and profitable distribution in our free enterprise system. In addition to the customary business considerations of marketing, production, and distribution, as well as financial and legal requirements, management must give first attention to the question of therapeutic merit. These are some of the questions that are asked about a proposed product:

Is there a need for the proposed product in the medical profession?

Does the product contribute something new? An improvement over existing products?

Is clinical evaluation necessary? Extensive? How long will it take? Cost?

In his speech, "Twixt the Cup and the Lip," before the American Medical Association last spring, Dr. Dowling 1 used a graphic diagram of the activities of the pharmaceutical industry. In words this diagram shows the idea being conceived—research and discovery. Following comes synthesis of the compound and laboratory studies of pharmacology and toxicology. If satisfactory, clinical trial is instituted. If the item is effective, safe and superior to existing therapy, the accumulated laboratory and clinical data are submitted to the Food and Drug Administration, U.S.A. If this agency finds no error in the data nor its translation into therapeutic claims, the drug is produced, packaged, distributed, and advertised to the practicing physician. The investigators report their findings at medical meetings. Prescriptions result in benefit to patients and profits to the company. Profits enable continued research in industrial and university laboratories. Except in the case of combination dosage forms convenient for patients, industry seldom deviates from this ideal procedure.

To survive in a highly competitive free-enterprise system, each pharmaceutical manufacturing company must continue to learn—just as medical practitioners must constantly add to their knowledge.

The industry must maintain modern, basic research laboratories which place emphasis on chemistry, bacteriology and pharmacology. In its major product areas each large company invests in fundamental research in basic science not only in its own laboratories but in the clinical departments of our universities and medical centers. In the pharmaceutical industry today exists the most efficient organization to apply the new discoveries from such research.

It is my conviction—and I believe it is shared by the responsible executives of our leading pharmaceutical houses—that nolle nocere today implies a knowledge of untoward effects. Such knowledge is just as essential to the successful therapeutic use of active pharmacologic agents as is an understanding of the desirable actions. We strive constantly to provide this kind of information to the medical profession.

The attitude of some physicians in assigning virtually all pharmaceutical

literature to the wastebasket is deplorable. For one thing, how can the industry warn you of newly recognized hazards? In all this speed-up and expansion of science, communications have become swamped. Publication is unable to keep pace with the expanded number of researchers and the great mass of data to be reported. We still rely on meetings and journals. This custom delays dissemination of important and often vital information for six to twenty-four months. The number of specialized societies and journals has multiplied alarmingly and is further fragmenting and scattering information at a time when we need assembling for both the researcher and the practicing clinician. Actually, the pharmaceutical industry is making a large contribution to the assembling of current, pertinent information on specific therapeutic problems. Surveys indicate that most clinicians commend rather than condemn the monographs prepared and distributed by the industry. Pharmaceutical literature—the direction circular—is often full of references listed as "In press," if actually accepted by a journal, or "Personal Communication," if not actually accepted for publication. Contrary to the implication of certain editors, these are not false references. These data—case reports and summaries—exist in the confidential files of the particular company and of the Food and Drug Administration. Your colleagues in pharmaceutical industry and government have judged the data adequate to substantiate all claims being made.

This spring in the field of physics in the United States it has become desirable for the American Physical Society ³ to issue a fortnightly newsletter, *Physical Review Letters*, in order to bring information submitted for publication rapidly to the attention of investigators in physics; and this type of rapid dissemination of information is being attempted in medicine in such magazines as *Medical Science* and *Modern Medicine*, presently being issued

semimonthly.

Being partially responsible for the direction of the resources of a large pharmaceutical firm, I feel—as do my fellow medical directors—a grave responsibility to the practicing physician for the accuracy and completeness of the information presented to him. And we are growing increasingly aware that the pharmacologic action of drugs and their associated untoward effects are the responsibility of the physician in the pharmaceutical industry. To be sure, we live in an era of advertising claims and counterclaims, but I can assure you that the statements made by reputable pharmaceutical companies in the multi-colored journal advertisements and mailing pieces are accurate. The Food and Drug Administration insists that claims remain within the bounds of the evidence presented to that body and that significant by-effects be brought to the attention of the prescribing physician.

Actually, the package insert, or direction circular, is a scientific document. More physicians should read it! Together with the laboratory and clinical evidence recorded by at least two clinicians, it has been studied with great

³ Editorial: Pitfalls of prepublication, Science 127: 623 (Mar. 21) 1958.

care by Drs. Holland, Smith and their associates in the Food and Drug Administration, and is your assurance that they have found no objections to the conclusions drawn nor to the data supporting those conclusions. Before being released, all new drugs must be demonstrated to be safe under the recommended conditions of use—dose, indications, and so forth. Although the law does not require proof of effectiveness in so many words, your guarantee is in the fact that an ineffective drug is not a safe drug when there are effective agents available for the condition, whatever it may be. Incidentally, it is unfortunate that so many physicians are apparently unaware of the effective labors of the dedicated group of physician-scientists in the Food and Drug Administration.

Today we live in a rapidly changing society. Health is big news. All of us who have anything to do with medicine live in a goldfish bowl and health news in the lay press creates problems—no doubt about it! But to attain the greatest good for all in our democracy, we must learn to live under this probing public scrutiny. We cannot go back to what some like to think of as the good old days. We must live in today's world, meeting today's problems with today's facilities while building for tomorrow in all aspects of medical care.

In summary, the pharmaceutical industry seeks to contribute to medical progress chiefly through the development and production of better therapeutic agents. This is its specific function as a member of the health team. The cost of a drug depends upon the costs of (a) research, (b) production, (c) rigid testing, and (d) distribution. As responsible citizens the managers of the industry within its resources also seek to contribute by means of basic research in our own laboratories, as well as by sponsored research in university laboratories, and by assistance to undergraduate and postgraduate educational efforts. Close collaboration between clinical investigators and the pharmaceutical industry is of mutual benefit and of great value to public health.

Here I shall quote briefly from the testimony of Dr. Nathan Kline, Research Director of the Rockland State Hospital of New York, at the recent Congressional inquiry into the marketing of tranquilizing drugs:

"Without the pharmaceuticals invented and prepared by the drug houses," Dr. Kline said, "it would have been impossible to achieve the promising results described. . . . These pharmaceuticals were not achieved by accident. It is one of the anomalies of our society that if a firm is successful in producing a product on which it can make money (which is in part used for the development of more such products) these researches are not regarded as being as scientifically 'pure' as work done in universities or other institutions. What is most peculiar about this is that we speak constantly of the advantages of a capitalistic free enterprise system and when we have overwhelming evidence of its successful functioning, we tend to disdain advances produced in this manner. The fact that commercial

enterprises are able to produce the high quality research results that they do should be a matter of great pride and recognition. The millions of dollars which are invested by drug manufacturing houses in an effort to find newer and more useful products is one of the most important factors which have made it possible for American science to hold such a prominent position in this field."

In this connection, it is evident that regulation of the pharmaceutical industry by pressure groups or self-appointed experts, even medical societies, is just as undesirable as would be such control of the practice of medicine. Effective and constructive regulation in our democratic society requires public responsibility on the part of the regulatory agency through open hearings and due process of law. At the same time, it is wise to recognize that both medicine and pharmacy need critics, and all should welcome criticism which is constructive and responsible.

We in the pharmaceutical industry appreciate the great responsibility we have toward the medical profession and to the public at large. And I should like to repeat that we need your collaboration, your help, if we are to share with all the members of the health team in contributing even more to the mutual benefit of medicine, pharmacy, and all mankind. In the common struggle against disease, all of us in the practice of medicine, pharmacy, and medical education are allies and we must provide mutual support to make the progress expected of us by society.

And now, as a physician in the pharmaceutical industry, let me assure you that our industry is striving to observe *nolle nocere* in its changing connotations.

GEORGE E. FARRAR, JR., M.D., F.A.C.P.

REVIEWS

Deficiency Diseases: Functional and Structural Changes in Mammalia Which Result from Exogenous or Endogenous Lack of One or More Essential Nutrients.

1st Ed. By Richard H. Follis, Jr., M.D. 577 pages; 26 × 18.5 cm. Charles C Thomas Company, Springfield, Illinois. 1958. Price, \$14.75.

This monograph develops naturally from the author's previous 1948 book, *The Pathology of Nutritional Disease*. In the earlier volume he restricted his discussion to those changes which could be ascribed to lack of a single nutrient. Those due to lack of multiple factors were excluded. In the present volume he broadens scope to discuss deficiencies due to multiple factors, as well as single nutrients, corresponding

to the natural state of most deficiency disease.

In his introduction the author outlines the course of the book, from inorganic to organic factors, to vitamins, to naturally-occurring deficiency disease, and to system involvement. By a clear and inescapably logical progression through preface to final page, the author conducts a considered scrutiny of his topic. Definitions are given, clearly and conservatively, at appropriate places. Specific and non-specific lesions are illustrated. The lucidity of the presentation and the appropriateness of the charts, pictures, and diagrams are outstanding.

Throughout the book emphasis is on that which is known. Many a paragraph ends with "this subject awaits further research" or "this door awaits opening and

future investigations."

The last two sections of the book, those on "Pathologic Physiology and Anatomy of Specific Tissues" and "Deficiency Disease as a Research Method of Biology and Medicine," are particularly notable. The former brings together in charts and under one head a correlation of nutritional factors and enzymatic activities in blood, muscle, and nerve tissues particularly helpful in integrating this complex area.

In the bibliography are 1535 references. There is an excellent Author Index

and a modest Subject Index to complete the volume.

So fundamental and reasoned is the author's conservative approach to this popular field that his book is recommended to students, interns, residents, and clinicians alike.

CONRAD BERENS ACTON, M.D.

Progress in Radiation Therapy. Edited by Franz Buschke, M.D.; with 13 contributors. 284 pages; 15.5 × 23.5 cm. Grune & Stratton, New York. 1958. Price, \$9.75.

The book has been edited by Dr. Franz Buschke, a world-renowned radiotherapist. It is presented in thirteen chapters; each chapter on a different subject by different authors.

As is any book written by many contributors, there are chapters which excel in the interest of the subject and the information given. Those written on the history of radiation therapy and radiation sources are full of interesting events related by people who lived them. These constitute a good source for information and reference.

The four chapters on radiobiology give good basic information about the funda-

mental principles of radiotherapy.

The chapter on cytologic evaluation of radiation response is a well-documented and well-written work giving just appreciation of the status of the problem today. The author cautions about the interpretation of the methods available at present, concluding that "at present, we do not have adequately proven, clinically useful means of predicting radiation response."

835

The chapter on renal embryoma is concise, clear, and has a very enlightening discussion on the possibilities and proper combination of the two main therapies, surgery and radiotherapy.

The two chapters on radiation therapy of the central nervous system are very well documented and give a good account of the problems of management, technic of treatment, and the dangers of complication in the irradiation of intracranial neoplasms.

The work on radiation therapy in carcinoma of the thyroid is an intelligent summary and "mis a point" of the present possibilities of all the therapeutic means in the management of these tumors. It contains a very timely word of caution about the indiscriminate use of radioiodine in the treatment of all thyroid carcinoma.

The chapter in radiotherapy of nonmalignant diseases of the eye is the reflection of the author's (Dr. Lederman) great experience, and it is of special interest for eye specialists and radiotherapists interested in the treatment of benign diseases of the eye.

The last chapter, Radiation Therapy as a Medical Specialty, is a defense of the

logical separation of Radiotherapy from Diagnostic Radiology.

The entire book, including the introduction, offers very useful and enlightening reading for the radiotherapist as well as for any other physician interested in the problem.

FERNANDO G. BLOEDORN, M.D.

Gynecologic and Obstetric Pathology, with Clinical and Endocrine Relations. 4th Ed. By EMIL NOVAK, A.B., M.D., D.Sc., F.A.C.S., F.R.C.O.G., and EDMUND R. NOVAK, A.B., M.D. 650 pages; 16.5 × 25.5 cm. W. B. Saunders Company, Philadelphia. 1958. Price, \$14.00.

Gynecologic and Obstetric Pathology is an outstanding work in its field and a standard text in the United States and abroad. This present fourth edition serves as a fitting memoir to its senior author, Dr. Emil Novak, recently deceased, a noted gynecologic pathologist and teacher.

The general format of this edition is the same as that of the third edition. Some of the chapters have been changed while others are new. The chapter on breast pathology has been deleted because, in the authors' opinion, the subject has been more thoroughly presented in other treatises. However, a completely new chapter on gynecologic cytopathology has been added. Within the last decade, cytodiagnosis has become an integral part of the diagnostic armamentarium of every physician. This chapter, written by Dr. John Frost, definitely enhances the value of the present edition.

In the third edition, obstetric pathology was detailed in two chapters. Dr. Robert Nesbitt has revised this material and combined it into a single chapter. The pages devoted to this subject are presented in a critical and forthright manner.

Opinions in this book are expressed in the light of present day concepts. The chapter dealing with carcinoma of the cervix has been almost completely revamped. The relationships between basal cell hyperplasia, "carcinoma in situ," and invasive carcinoma have been clarified.

This edition has been expanded to the extent of 55 pages. The quality of the paper has been improved and the illustrations have been increased in number. Mention should be made that there is a lack of microscopic detail in some of the authors' plates. These same plates have appeared in previous editions and their full sharpness and clarity have decreased with repeated printings.

In spite of a few criticisms, this book is indeed a near classic text. For those interested in the pathology of the female genital tract it serves as an excellent

reference book.

Fundamentals of Electrocardiography and Vectorcardiography. By LAWRENCE E. LAMB, M.D., Director of Cardiology, Air University, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas. 142 pages; 22 × 28.5 cm. Charles C Thomas, publisher, Springfield, Ill. 1957. Price, \$9.50.

As the preface states, it is the purpose of this book to set forth the basic fundamentals of electrocardiography and vectorcardiography. Included are chapters devoted to fundamental vector and cellular concepts, the heart as a source of electrical forces, fundamentals of conductors, electrocardiographic instruments and leads, normal electrocardiograms, fundamentals of vectorcardiography, and abnormal tracings. There are profuse illustrations and a detailed index, but a scant bibliography. The text tends to be abstruse and the illustrations, particularly the vectorcardiograms, are at times inadequately labeled.

The author includes several interesting and original observations including an apparent relationship of increased heart rate and smaller QRS amplitude. He states that the electrocardiogram is a sensitive measurement of the changes in right ventricular and left ventricular stroke volume. With inspiration, there is a progressive decrease in ORS amplitude in all leads.

This text reflects the ever growing interest in vectorcardiography and the basic fundamentals of electrocardiography. Of importance is the emphasis upon an integrated approach to the electrical activity of the heart and the need for an organized concept in interpretation rather than pattern analysis.

L. S.

The Neurologic Examination, Incorporating the Fundamentals of Neuroanatomy and Neurophysiology. 2nd Ed. By Russell N. DeJong, M.D. 1078 pages; 18 × 26 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1958. Price, \$20.00.

This is the second edition of this well-known treatise. The new edition preserves the same manner of presentation as the first edition and contains essentially the same material. The only changes appear to be in the areas of physiology and anatomy—and these changes are not too extensive. Even these few alterations, sufficient to keep abreast with newer developments, have required some rewriting. The illustrations are numerous and, with the exception of a few additions, the same as in the first edition.

The format of this volume is that of most treatises of the neurologic examination presenting first a discussion of the history, mental examination, and the general physical examination. Then in the following order there are sections devoted to the sensory system, the cranial nerves, the motor system, the reflexes, the autonomic nervous system, diagnosis and localization of the spinal axis and of intracranial disease. Finally, disturbances of consciousness, hysteria and the cerebrospinal fluid are discussed. Throughout the volume every effort is made to correlate the technics of the neurological examination with the anatomy and physiology involved in each part of the examination. In addition, every effort has been made to present as complete a discussion of the subject as possible. There is an up-to-date list of references to the literature at the end of most chapters, there being in all 61 chapters. In addition to these bibliographies there is, at the close of the volume, a list of general references divided into a section on clinical neurology and one on anatomy, physiology and pathology. Finally, there is a useful and apparently complete index.

The resulting size of the volume will be somewhat disturbing to the average medical student who will probably only use it occasionally as a reference work. Its completeness recommends it for such a role. Aside from its size, the only other

criticism which can be made of this book is the price, which will also discourage some medical students. It is the opinion of this reviewer that this work is a valuable addition to the library of anyone who is engaged in the practice of clinical neurology, psychology, or neurosurgery. As a reference work it should be available for the use of all medical students.

C. V. B.

Study Group on Pediatric Education. World Health Organization Technical Report Series No. 119. 20 pages; 16 × 24 cm. (paper-bound). World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. 1957. Price, 30 cents.

This is a report from the World Health Organization of a conference on pediatric education held in Stockholm in the summer of 1956, July 30 to August 4.

The topics discussed were inclusive of various phases of undergraduate, graduate and postgraduate teaching as to content, methodology, time allotment, organization and correlation with other departments.

Information from certain countries indicates that child care accounts for at least one-third of total medical practice and, in some countries, the proportion is even greater. However, the time assigned to pediatrics in the medical curriculum is often insufficient to cover the subject matter and technical knowledge involved.

The group expressed the opinion that all pediatricians should take an active part in communal health work, fostering research and assessing and improving conditions in the community.

The report should be of special interest to administrators of medical schools and all chairmen of medical school departments.

J. E. B.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

- L'Année Oto-rhino-laryngologique 1958. Par A. Aubin et M. Bouchet; Comité de Rédaction: R. Maduro, M. Aubry, J.-J. Debain; Secrétaires: J. Bouche, P.-L. Klotz. 197 pages; 25.5 × 16.6 cm. (paper-bound). 1958. Masson & Cie, and Librairie Arnette, Paris. Price, 1.600 fr.
- The Chemical Prevention of Cardiac Necroses. By HANS SELYE, M.D., Ph.D., D.Sc., Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada. 235 pages; 24 × 15.5 cm. 1958. The Ronald Press Company, New York. Price, \$7.50.
- Chloromycetin (Chloramphenicol). Antibiotics Monographs No. 8. (Under the editorial direction of Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.) By Theodore E. Woodward, M.D., and Charles L. Wisseman, Jr., M.D., University of Maryland School of Medicine, Baltimore, Maryland; with the collaboration of Harry M. Robinson, Jr., M.D., George Entwisle, M.D., Fred R. McCrumb, Jr., M.D., and Merrill J. Snyder, Ph.D.; foreword by Joseph E. Smadel, M.D. 159 pages; 23.5 × 16 cm. 1958. Medical Encyclopedia, Inc., New York. Price, \$4.00.

- Clinical Chemistry in Practical Medicine. 5th Ed. By C. P. Stewart, D.Sc. (Dunelm.), Ph.D. (Edin.), Reader in Clinical Chemistry, University of Edinburgh, etc.; and D. M. DUNLOP, B.A. (Oxon.), M.D., F.R.C.P. (Edin.), F.R.C.P. (Lond.), Christison Professor of Therapeutics and Clinical Medicine, University of Edinburgh, etc. 342 pages; 22 × 14 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$6.75.
- Clinical Epidemiology (The Scientist's Library: Biology and Medicine, edited by Peter P. H. De Bruyn, M.D.). By John R. Paul, M.D., Sc.D., Professor of Preventive Medicine, Yale University School of Medicine. 291 pages; 22 × 14.5 cm. 1958. The University of Chicago Press, Chicago. Price, \$5.00.
- Cold Injury: Transactions of the Fifth Conference, March 10, 11, 12, 13, 14, and 15, 1957, Arctic Aeromedical Laboratory, Ladd Air Force Base, Alaska. Edited by M. Irené Ferrer, M.D., Assistant Professor of Clinical Medicine, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 341 pages; 24 × 16 cm. 1958. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$5.95.
- La Cortisone et l'A.C.T.H. en Oto-rhino-laryngologie. Société Francaise d'Oto-rhino-laryngologie. Par A. Aubin, J. Terracol et Y. Guerrier. 158 pages; 24 × 15.5 cm. (paper-bound). 1958. Librairie Arnette, Paris. Price, 2.000 fr.
- Counseling Parents of Children with Mental Handicaps: Proceedings of the 33rd Spring Conference of the Woods Schools, Held in Minneapolis, May 2 and 3, 1958. 108 pages; 22.5 × 15.5 cm. (paper-bound). 1958. Sponsored by The Woods Schools for Exceptional Children, Langhorne, Pa. Price: Single copy available without charge; additional single copies, \$1 each; 2 to 9 copies, 75¢ each; 10 to 49 copies, 65¢ each; 50 to 99 copies, 60¢ each; 100 copies or over, 50¢ each.
- Differentialdiagnose Innerer Krankheiten. Von Dr. Robert Hegglin. 819 pages; 24.5 × 17.5 cm. 1959. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 79.50.
- The Ecology of the Medical Student: Report of the Fifth Teaching Institute, Association of American Medical Colleges, Atlantic City, New Jersey, October 15-19, 1957. Edited by Helen Hofer Gee and Robert J. Glaser, with the assistance of the Planning Committee; editorial coordination by E. Shepley Nourse. 287 pages; 25 × 17.5 cm. 1958. Published for the Fifth Teaching Institute on The Ecology of the Medical Student as Part 2 of the Journal of Medical Education, October 1958, by the Association of American Medical Colleges, Evanston, Illinois. Price, clothbound, \$3.00; paperbound, \$2.00.
- Handbuch der Virusforschung. Begrundet von Prof. Dr. R. Doerr und Prof. Dr.
 C. Hallauer. 4. Band (III. Erganzungsband). Herausgegeben von Prof. Dr.
 C. Hallauer und Prof. Dr. K. F. Meyer. 688 pages; 25 × 17.5 cm. 1958.
 Springer-Verlag, Vienna. Price, \$35.25.
- Insect Resistance and Vector Control: Eighth Report of the Expert Committee on Insecticides. World Health Organization Technical Report Series No. 153.
 68 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, \$0.60.

- International Medical Research: A Compilation of Background Materials, Prepared for the Committee on Government Operations, United States Senate, and Its Subcommittee on Reorganization and International Organizations, Pursuant to S. Res. 347, 85th Congress, November 10, 1958. Committee Print, 85th Congress, 2d Session. 117 pages; 23.5 × 15 cm. (paper-bound). 1958. United States Government Printing Office, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 45¢.
- Joint FAO/WHO Expert Committee on Nutrition: Fifth Report. World Health Technical Report Series No. 149. 55 pages; 24 × 16 cm. 1958. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60¢.
- Leukemia. By WILLIAM DAMESHEK, M.D., Professor of Medicine, Tufts University School of Medicine, etc.; and Frederick Gunz, M.D., Ph.D., Hematologist, Christchurch Hospital, Christchurch, New Zealand, etc. 420 pages; 26 × 18 cm. 1958. Grune & Stratton, New York. Price, \$15.75.
- Lipidoses: Diseases of the Intracellular Lipid Metabolism. 3d Ed. By Siegfried J. Thannhauser, M.D., Ph.D., Hon. M.D., Universities of Freiburg, Munich, Dusseldorf, Clinical Professor of Medicine Emeritus, Tufts College Medical School, Boston, etc. 600 pages; 24.5 × 18 cm. 1958. Grune & Stratton, New York. Price, \$19.75.
- Makroglobulinämie Waldenström. Herausgegeben von G. Riva, Bern; unter Mitarbeit von A. Hässig, Bern; F. Heinzler, Düsseldorf; H. Isliker, Bern; K. Jahnke, Düsseldorf; R. Kappeler, Bern; A. Krebs, Bern; J. J. Scheidegger, Genf; W. Scholtan, Wuppertal; R. Weber, Bern, und H. U. Zollinger, St. Gallen; mit einer Einleitung von Karl Rohr, Zürich. 183 pages; 24 × 16 cm. (paperbound). 1958. Benno Schwabe & Co. Verlag, Basel/Stuttgart; sole representative for U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, \$4.25.
- Modern Chemotherapy of Tuberculosis. Antibiotics Monographs, No. 11 (under the Editorial Direction of Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.). By Roger S. Mitchell, B.A., M.D., F.A.C.P., and J. Carroll Bell, B.S., M.D., M.S., F.A.C.P., The Colorado Foundation for Research in Tuberculosis and the University of Colorado School of Medicine, Denver, Colorado; foreword by William B. Tucker, M.D. 109 pages; 23.5 × 16 cm. 1958. Medical Encyclopedia, Inc., New York. Price, \$4.00.
- Muir's Text-Book of Pathology. 7th Ed. Revised by D. F. CAPPELL, C.B.E., M.D., F.R.F.P.S., M.R.C.P., F.R.S.Ed., Professor of Pathology, University of Glasgow, etc. 1,201 pages; 24 × 15.5 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$14.50.
- Nutrition and Atherosclerosis. By Louis N. Katz, M.D., Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, etc.; Jeremiah Stamler, M.D., Previously Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, etc.; and Ruth Pick, M.D., Assistant Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois, etc. 146 pages; 24 × 15.5 cm. 1958. Lea & Febiger, Philadelphia. Price, \$5.00.

- Obstetric and Gynecologic Milestones. Essays in Eponymy. By Harold Speert, M.D., Assistant Professor of Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, etc. 700 pages; 23.5 × 16 cm. 1958. The Macmillan Company, New York. Price, \$15.00.
- Penicillin. Antibiotics Monographs No. 9. (Under the Editorial Direction of Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.) By Harold L. Hirsh, M.D., and Lawrence E. Putnam, M.D., Washington, D.C.; foreword by Harry F. Dowling, M.D. 148 pages; 23.5 × 16 cm. 1958. Medical Encyclopedia, Inc., New York. Price, \$4.00.
- Problems of Addiction and Habituation. The Proceedings of the Forty-seventh Annual Meeting of the American Psychopathological Association, Held in New York City, February 1957. Edited by Paul H. Hoch, M.D., New York State Psychiatric Institute, etc.; and Joseph Zubin, Ph.D., New York State Psychiatric Institute, etc. 250 pages; 22.5 × 14.5 cm. 1958. Grune & Stratton, New York. Price, \$6.50.
- Reversible Renal Insufficiency: Diagnosis and Treatment. By Donald H. Atlas, M.D., Ph.D., F.A.C.P., Associate Professor of Medicine, Northwestern University School of Medicine, etc.; and Peter Gaberman, M.D., Late Associate Professor of Medicine, The Chicago Medical School, etc. 233 pages; 22.5 × 15 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, \$7.00.
- Selected Survey Topics, United States, July 1957-June 1958: Selected Statistics Relating to Days of Disability, Acute Conditions, Chronic Conditions, Persons Injured, Physician Visits, and Dental Visits. Based on Data Collected in Household Interviews During July 1957-June 1958. Health Statistics from the U.S. National Health Survey, Public Health Service Publication No. 584-B5. 49 pages; 26 × 20 cm. (paper-bound). 1958. U.S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington 25, D. C., at 40¢.
- Serologie und Klinische Bedeutung der Autohämantikörper. Von H. Schubothe; mit einem Geleitwort von L. Heilmeyer. 284 pages; 25 × 17.5 cm. (paperbound). 1958. S. Karger, Basel. Price, sFr. 36.—.
- Streptomycin and Dihydrostreptomycin. Antibiotics Monographs No. 10. (Under the Editorial Direction of Henry Welch, Ph.D., and Félix Martí-Ibáñez, M.D.) By Louis Weinstein, Ph.D., M.D., Professor of Medicine, Tufts University School of Medicine, etc.; and N. Joel Ehrenkranz, M.D., Assistant Professor of Medicine, University of Miami School of Medicine, etc.; foreword by Chester S. Keefer, M.D. 116 pages; 23.5 × 16 cm. 1958. Medical Encyclopedia, Inc., New York. Price, \$4.00.
- Traitement du Cancer de la Base de la Langue. Société Française d'Oto-rhinolaryngologie. Par P.-C. Huet, M. Gignoux, F. Bérard, P. Andre et J. La-Bayle, avec la collaboration de J. Pinel et J. Siardet. 235 pages; 24 × 15.5 cm. (paper-bound). 1958. Librairie Arnette, Paris. Price, 3.000 fr.
- Tumors of the Lungs and Mediastinum. By B. F. Fried, M.D., F.C.C.P., Associate Attending Physician, Montefiore Hospital, etc. 467 pages; 24 × 15.5 cm. 1958. Lea & Febiger, Philadelphia. Price, \$13.50.

- Understanding Aphasia: A Guide for Family and Friends. Patient Publication No. 2, The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. By Martha L. Taylor, M.A., Chief, Department of Speech and Hearing Therapy, Institute of Physical Medicine and Rehabilitation, Instructor, Department of Physical Medicine and Rehabilitation of the New York University College of Medicine; foreword by Howard A. Rusk, M.D. 48 pages; 21.5 × 14 cm. (paper-bound). 1958. The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York. Price, 50¢.
- Unsaturated Fats and Serum Cholesterol, With Special Emphasis on Corn Oil. By DOROTHY M. RATHMANN, Ph.D., Technical Division, Corn Products Refining Company, Argo, Illinois. 47 pages; 24 × 17.5 cm. (paper-bound). 1958. Corn Products Refining Company, New York. Free on request.
- Young Endeavour: Contributions to Science by Medical Students of the Past Four Centurics. By William Carleton Gibson, D.Phil. (Oxon.), M.D., C.M., Kinsmen Professor of Neurological Research, University of British Columbia; with a foreword by Sir Henry Dale, O.M. 292 pages; 24 × 16 cm. 1958. Charles C Thomas, Publisher, Springfield, Illinois. Price, \$6.50.

COLLEGE NEWS NOTES

NEW LIFE MEMBERS

The College acknowledges with pleasure the following new Life Members:

Dr. Charles Bohnengel, Toledo, Ohio

Dr. Marvin B. Day, Hartford, Conn.

Dr. Charles F. Downing, Decatur, Ill.

Dr. Arthur F. Edwardes, Los Angeles, Calif.

Dr. Lawrence H. Gahagan, New York, N. Y.

Dr. Samuel B. Hadden, Philadelphia, Pa.

Dr. John D. Hallahan, Media, Pa.

Dr. Irving I. Lasky, Beverly Hills, Calif.

Dr. Irene F. Laub, Easton, Pa.

Lt. Col. William H. Meroney, (MC), USA

Dr. C. Edward Rankin, Lexington, Ky.

Dr. Albert Segaloff, New Orleans, La.

Dr. David C. Thurber, Rochester, N. Y.

Dr. Harry F. Zinsser, Philadelphia, Pa.

BOOKS DONATED TO THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

The College gratefully acknowledges receipt of the following books from members of the College to the Memorial Library of Publications by Members of the College:

- William Bennett Bean, M.D., F.A.C.P., Iowa City, Iowa, VASCULAR SPIDERS AND RELATED LESIONS OF THE SKIN, published by Charles C Thomas, Springfield, Ill., 1958, 372 pages.
- Roger I. Lee, M.D., M.A.C.P., Boston, Mass., A DOCTOR SPEAKS HIS MIND, published by Little, Brown & Co., Boston and Toronto, 1958, 120 pages.
- Karl Menninger, M.D., F.A.C.P., Topeka, Kans., THEORY OF PSYCHOANA-LYTIC TECHNIQUE, published by Basic Books, Inc., New York, N. Y., 1958, 206 pages.
- William B. Sherman, M.D., F.A.C.P., New York, N. Y., ALLERGY IN PEDI-ATRIC PRACTICE, published by C. V. Mosby Co., St. Louis, Mo., 1957, 296 pages.
- Solomon Silver, M.D., F.A.C.P., New York, N. Y., RADIOACTIVE ISOTOPES IN CLINICAL PRACTICE, published by Lea & Febiger, Philadelphia, Pa., 1958, 451 pages.
- Ian Maclean Smith, M.D., (Associate), Iowa City, Iowa, STAPHYLOCOCCAL INFECTIONS, published by The Year Book Publishers, Inc., Chicago, Ill., 1958, 180 pages.
- John H. Talbott, M.D., F.A.C.P., and L. Maxwell Lockie, M.D., F.A.C.P., Buffalo, N. Y., PROGRESS IN ARTHRITIS, published by Grune & Stratton, New York and London, 1958, 456 pages.

THREE FELLOWS RECEIVE NATIONAL HONOR

Among the ten leaders of American Medicine to receive the distinguished achievement awards made by the Board of Medical Editors of Modern Medicine, an international medical publication, were the following Fellows of the College: Dr. Robert

F. Loeb, Bard Professor of Medicine at Columbia University College of Physicians and Surgeons and Director of Medical Service at the Presbyterian Hospital, New York, N. Y., for "Investigations of electrolyte physiology and the adrenocortical relationship to salt and water metabolism and an outstanding career as teacher and clinician"; Dr. Cecil J. Watson, Professor of Medicine and Chairman of the Department of Medicine, University of Minnesota Medical School, Minneapolis, Minn., for "his additions to the clinical knowledge of liver function and the clarification of porphyrin metabolism," and Dr. W. Barry Wood, Jr., Professor of Microbiology, The Johns Hopkins University School of Hygiene and Public Health and Vice President of Johns Hopkins University, for "Research concerning the pathogenesis of fever and leadership in exploring new methods of medical education." The recipients were selected from entries of medical researchers, teachers and clinicians nominated by deans of medical schools and readers of the journal.

INTERSTATE COMPACT ON MENTAL HEALTH

There now are 12 states which have enacted the Interstate Compact on Mental Health. These are: Connecticut, Kentucky, Louisiana, Maine, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Oregon, Rhode Island, and West Virginia. This year the compact is being considered by legislative committees in a number of states, including Arkansas, Indiana, Michigan, Missouri, Oklahoma, and Texas.

The Interstate Compact on Mental Health has as its purpose solving the problem of hospitalizing the nonresident mental patient. Its aim is to apply medical judgment to the proper hospitalization of a patient rather than narrow residence requirements. It also permits interstate supervision of convalescent patients as well as pooling of facilities among states.

The Compact Administrators of the states which have adopted the compact will be meeting at the Bellevue Stratford Hotel in Philadelphia, Pa., on Sunday, April 26, 1959, the day before the American Psychiatric Association opens its annual meeting, for a morning session, starting at 10:00 a.m. At 2:00 p.m. the same day, there will be a general session open to anyone interested, for a discussion of the Compact and its operation. Information on the Compact can be obtained from Mr. Sidney Spector, Council of State Governments, 1313 E. 60th St., Chicago 37, Ill.

1959 MISSISSIPPI VALLEY MEDICAL SOCIETY ESSAY CONTEST

The attention of physician-medical writers is called to the Mississippi Valley Medical Society Annual Essay Contest. Any subject of general medical or surgical interest including medical economics and education may be submitted, provided the paper is unpublished and is of interest and applicable value to general practitioners of medicine. Contributions are accepted only from physicians who are members of the A.M.A. and who are residents and citizens of the United States. Manuscripts must not exceed 5000 words and be submitted in 5 complete copies, in manuscript style. The winning essay receives a cash prize of \$100.00, a gold medal, and a certificate, also an invitation to address the annual meeting of the Mississippi Valley Medical Society (held at time and place of the American Medical Writers' Association; 1959 meeting, St. Louis, Sept. 30, Oct. 1, 2). The Society may also award certificates of merit to physicians whose essays rate second and third best. Essays must be in the office of the Secretary not later than May 1, 1959. Winning essays are published each year in the January Mississippi Valley Medical Journal (Quincy, Ill.). Further details may be secured from Harold Swanberg, M.D., Secretary, MVMS, 209-224 W.C.U. Bldg., Quincy, Ill.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY ANNOUNCES EXAMINATIONS

The American Board of Psychiatry and Neurology will conduct two examinations to be given later in 1959: Chicago, Ill., October 19-20; New York, N. Y., December 14-15. For information, write David A. Boyd, Jr., M.D., Secretary-Treasurer, American Board of Psychiatry and Neurology, Inc., 102-110 2nd Ave., S.W., Rochester, Minn.

AMERICAN COLLEGE OF GASTROENTEROLOGY AWARD CONTEST

The American College of Gastroenterology announces the establishment of an award contest for the best unpublished paper on research in gastroenterology or an allied field. This award is to be known as the Henry G. Rudner, Sr., Award, honoring Henry G. Rudner, Sr., F.A.C.P., Memphis, Tenn., Chairman of the Research Committee of the American College of Gastroenterology and Former Chairman of the Board of Governors of the organization. The prize will be an award of \$750.00 plus an additional \$250.00 for traveling expenses to present the paper at the 24th Annual Convention of the College.

The contest is open to all those possessing the degree of Doctor of Medicine from a recognized medical school or university. All papers submitted must represent original work in gastroenterology, or an allied field, and must not have been previously published except for abstracts or short preliminary reports. It must not have been previously presented on the program of any scientific meeting. The contents of the papers can be clinical or basic science. Clinical papers must not be case records, but controlled clinical work.

All entries for the 1959 award must be typewritten in English, double-spaced on one side of the paper and submitted in six copies. The winning entry will be selected by the Research Committee of the American College of Gastroenterology and the award will be made at the Annual Convention Banquet of the College, to be held in Los Angeles, Calif., in September of 1959. Entries must be received no later than June 1, 1959, and should be addressed to: The Research Committee, American College of Gastroenterology, 33 W. 60th St., New York 23, N. Y.

CANADIAN COUNCIL ON HOSPITAL ACCREDITATION

On January 17, 1959, hospital and medical officials met at the Canadian Medical Association House in Toronto, Ont., to inaugurate the first all-Canadian program designed to improve and develop the standard of hospital care in Canada.

The program will be under the direction of the newly-formed Canadian Council on Hospital Accreditation; and its main objective is to provide the hospital patient with the best possible treatment and care within the power of hospital and medical science. The function of the program is to survey hospitals at their request, to ensure the welfare and safety of the patient. Every aspect of hospital administration and operation will be examined by the physician surveyor. If the survey report meets the approval of the Council, the hospital concerned will be certified as an accredited hospital.

FIRST INTERNATIONAL CONGRESS ON MENTAL RETARDATION

The First International Medical Conference on Mental Retardation, organized by the Maine Chapter of the American Academy of Pediatrics, The Division of Maternal and Child Health, the Maine Department of Health and Welfare and the Pineland Hospital and Training School, Pownal, Maine, will be held from July 27–31, 1959, at Portland, Maine.

The program will include in its five days of general sessions, addresses on brain anatomy, the reticular system, head anomalies, phenylketonuria, lipoids, birth injury, embryology, infections, mongolism, erythroblastosis, therapy, psychiatry, psychology, and behavior disorders, by outstanding authorities on these subjects.

Not intended to answer all questions on the problems concerning mental retardation, but rather to construct the problems which have to be attacked scientifically, the conference is open to all physicians throughout the United States, Canada, and other countries of the world. It follows immediately after the International Pediatric Congress at Montreal, Canada.

Write Ella Langer, M.D., State of Maine Department of Health and Welfare, Augusta, Maine.

3RD INTERNATIONAL CONGRESS OF SCHOOL AND UNIVERSITY HEALTH

The 3rd International Congress of School and University Health sponsored by the International Association of Universities, the International Association for Educational and Vocational Information, and the French Ministry of Education and Ministry of Health, will be held in the Unesco House, Place Fontenoy, Paris, France, July 6–8, 1959. The program will include the subjects: "Infectious Diseases in School," "School Environment and Child Health," and "Epilepsy in School."

During the Congress, representatives of the associations will meet to discuss the statutes of the International Union of School and University Health and Medical Services which have been under consideration for several years.

For information, write the Organizing Committee, 3rd International Congress of School and University Health, 13, rue du Four, Paris-6, France.

13th General Assembly Program

The Canadian Medical Association will be host to the 13th General Assembly of the World Medical Association to be convened in Montreal, Canada, September 7-12, 1959. The tentative program includes: (1) Medical Editors' Conference; (2) Socio-Medical Affairs; (3) Scientific Program; (4) Tours of Montreal Medical Institutions, and (5) Technical and Scientific Exhibits. Write to the Secretary General, The World Medical Association, 10 Columbus Circle, New York 19, N. Y.

AMA ADMINISTRATION REORGANIZED

A number of major changes have been made recently in the administrative structure of the American Medical Association in an effort to streamline and strengthen the organization.

For administrative purposes, AMA's headquarters staff has been divided into seven divisions: (1) A Business Division, headed by Business Manager Russell H. Clark, includes advertising and circulation departments of AMA publications, as well as all other business activities; (2) A Law Division, headed by C. Joseph Stetler; (3) A Communications Division, headed by Leo Brown, will coordinate for the first time under one management all methods of communication—press, radio, television, films, and exhibits; (4) A Field Division, under the direction of Aubrey Gates, with a staff of four field representatives will serve as a link between AMA and the grass roots; (5) A division of Scientific Publications includes editorial departments of all of the association's scientific journals. Dr. J. F. Hammond, Associate Editor of the Journal of the American Medical Association, replaced Dr. Austin Smith who resigned as editor, and (6-7) The remaining two divisions, Socio-Economic Activities and

Scientific Activities, still are in the process of development and are temporarily under the direction of Dr. Ernest B. Howard, Assistant Executive Vice President.

FORM NEW FOUNDATION IN FIELD OF PSYCHIATRY

Dr. Everett C. Fox, F.A.C.P., and Dr. Perry C. Talkington, (Associate), both of Dallas, Tex., are members of the Board of Trustees of the newly-formed Timberlawn Foundation. The Foundation will extend the work already being conducted at the Timberlawn Sanitarium in Dallas, Tex., which is the oldest psychiatric private hospital in the Southwest. The principal objective of the Foundation is the furtherance of education in research and psychiatry, but the immediate aims are the training of five first-year resident psychiatrists, three second-year residents, one research assistant, and three occupational and recreational therapy students.

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL ESTABLISHES TWO PROFESSORSHIPS IN NUTRITION AND METABOLISM

Endowments of two professorships for a half million dollars each have been made possible through the work of the Spies Committee for Clinical Research which has been formed to support the work of nutrition begun by Dr. Tom D. Spies, F.A.C.P., Professor and Chairman of the Department of Nutrition and Metabolism at the Northwestern Medical School. The first chair was named "The Tom D. Spies Professor of Nutrition and Metabolism" and Dr. Robert E. Stone, F.A.C.P., was named to this post. The second professorship, as yet unnamed, will be held by Dr. Spies. In announcing the establishment of the professorships, Dr. Richard H. Young, F.A.C.P., Dean of the Northwestern Medical School, said, "The support given to universities by the endowment of professorships such as these assures financial stability for vital research projects and represents an investment not in individuals, but in the work of scientists striving to make life happier, healthier, and longer."

HOWARD W. BLAKESLEE AWARDS COMPETITION FOR 1959

The opening of the 7th Annual Competition for the Howard W. Blakeslee Awards for outstanding reporting in the field of heart and blood vessel diseases was announced today by the American Heart Association. Selections from among newspaper and magazine articles, books, radio and television programs and films published or produced between March 1, 1958, and February 28, 1959, will be made by the Heart Association's Blakeslee Awards Committee. May 1, 1959, will be the deadline for entries.

Entries submitted by local daily or weekly newspapers, and local radio and television stations will be considered on the same basis as entries from national wire services, syndicates or radio-TV networks, and they will be eligible for awards in separate categories. The number of winners to be selected will be determined by the judges. The awards carry an honorarium of \$500 each.

Entry blanks and rules folders may be obtained from local Heart Associations or from the American Heart Association, 44 E. 23rd St., New York 10, N. Y.

NATIONAL MEDICAL MEETINGS, APRIL-SEPTEMBER, 1959

April

AERO MEDICAL ASSOCIATION, Hotel Statler, Los Angeles, Calif., April 27-29. Dr. Thomas H. Sutherland, Secretary, P. O. Box 26, Marion, Ohio.

- AMERICAN ACADEMY OF NEUROLOGY, Hotel Statler, Los Angeles, Calif., April 13-18. Dr. Joseph M. Foley, Secretary, Boston City Hospital, Boston, Mass.
- AMERICAN ASSOCIATION OF IMMUNOLOGISTS, Atlantic City, N. J., April 13-17. Dr. Calderon Howe, Secretary, 630 W. 168th St., New York 32, N. Y.
- AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS, Somerset Hotel, Boston, Mass., April 23–25. Dr. Russell L. Holman, Secretary, 1542 Tulane Ave., New Orleans 12, La.
- AMERICAN COLLEGE OF PHYSICIANS, Conrad Hilton Hotel, Chicago, Ill., April 20-24. Mr. E. R. Loveland, Executive Secretary, 4200 Pine St., Philadelphia 4. Pa.
- AMERICAN GOITER ASSOCIATION, Chicago, Ill., April 30-May 2. Dr. John C. McClintock, Secretary, 149½ Washington Ave., Albany, N. Y.
- AMERICAN PHYSIOLOGICAL SOCIETY, Atlantic City, N. J., April 12-16. Dr. Ray G. Daggs, Executive Secretary, 9650 Wisconsin Ave., Washington, D. C.
- AMERICAN PSYCHIATRIC ASSOCIATION, Civic Auditorium, Philadelphia, Pa., April 27-May 1. Dr. C. H. Hardin Branch, Secretary, 156 Westminster Ave., Salt Lake City, Utah.
- AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY, Atlantic City, N. J., April 13-18. Dr. J. F. A. McManus, Secretary, University of Alabama Medical Center, Birmingham 3, Ala.
- AMERICAN SOCIETY OF INTERNAL MEDICINE, Conrad Hilton Hotel, Chicago, Ill., April 19. Dr. Clyde C. Greene, Jr., Assistant Secretary, 350 Post St., San Francisco 8, Calif.
- AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, Atlantic City, N. J., April 13-17. Dr. Harold Hodge, Secretary, University of Rochester, Rochester 20, N. Y.
- AMERICAN SOCIETY FOR THE STUDY OF STERILITY, Shelburne Hotel, Atlantic City, N. J., April 3-5. Dr. Herbert H. Thomas, Secretary, 920 S. 19th St., Birmingham 5, Ala.
- AMERICAN VENEREAL DISEASE ASSOCIATION, Johns Hopkins University, Baltimore, Md., April 27-28. Dr. S. Ross Taggart, Secretary-Treasurer, 1325 Upshur St., N.W., Washington 11, D. C.
- INDUSTRIAL MEDICAL ASSOCIATION, Sherman Hotel, Chicago, Ill., April 26-29. Dr. Leonard Arling, Secretary, 3101 University Ave., S.E., Minneapolis 14, Minn.

May

- AMERICAN ASSOCIATION FOR THE HISTORY OF MEDICINE, Wade Park Manor, Cleveland, Ohio, May 21-23. Dr. John B. Blake, Secretary, Smithsonian Institution, Washington 25, D. C.
- AMERICAN ASSOCIATION ON MENTAL DEFICIENCY, Hotel Schroeder, Milwaukee, Wis., May 19-23. Dr. Neil A. Dayton, Secretary-Treasurer, Mansfield State Training School and Hospital, Mansfield Depot, Conn.
- AMERICAN COLLEGE OF CARDIOLOGY, Benjamin Franklin Hotel, Philadelphia, Pa., May 26-29. Dr. Philip Reichert, Secretary, 480 Park Ave., New York 22, N. Y.
- AMERICAN FEDERATION FOR CLINICAL RESEARCH, Chalfonte-Haddon Hall, Atlantic City, N. J., May 3. Dr. George E. Schreiner, Secretary, Georgetown University Hospital, Washington 7, D. C.
- AMERICAN PEDIATRIC SOCIETY, The Inn, Buck Hill Falls, Pa., May 6-8. Dr. A. C. McGuinness, Secretary, 2800 Quebec St., Washington 8, D. C.

- AMERICAN PSYCHOSOMATIC SOCIETY, Chalfonte-Haddon Hall, Atlantic City, N. J., May 2-3. Dr. Morton F. Reiser, Secretary, 265 Nassau Rd., Roosevelt, N. Y.
- AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Haddon Hall, Atlantic City, N. J., May 3-4. Dr. S. J. Farber, Secretary, 550 1st Ave., New York
- AMERICAN TRUDEAU SOCIETY, Palmer House, Chicago, Ill., May 25-27.
- Dr. E. P. K. Fenger, Secretary, 1790 Broadway, New York 19, N. Y. ASSOCIATION OF AMERICAN PHYSICIANS, Haddon Hall, Atlantic City, N. J., May 5-6. Dr. Paul B. Beeson, Secretary, Yale University School of Medicine, New Haven 11, Conn.
- NATIONAL TUBERCULOSIS ASSOCIATION, Palmer House, Chicago, Ill., May 24-29. Mrs. Wallace B. White, Secretary, 1790 Broadway, New York 19,
- SOCIETY OF AMERICAN BACTERIOLOGISTS, Sheraton Jefferson Hotel, St. Louis, Mo., May 10-15. Dr. E. M. Foster, Secretary, University of Wisconsin, Madison 6, Wis.

June

- AMERICAN COLLEGE OF CHEST PHYSICIANS, Atlantic City, N. J., June 3-7. Mr. Murray Kornfeld, Executive Director, 112 E. Chestnut St., Chicago 11, III.
- AMERICAN DERMATOLOGICAL ASSOCIATION, Claridge Hotel, Atlantic City, N. J., June 1-4. Dr. Wiley M. Sams, Secretary, 25 Southeast 2nd Ave., Miami, Fla.
- AMERICAN DIABETES ASSOCIATION, Chalfonte-Haddon Hall, Atlantic City, N. J., June 6-7. Dr. E. Paul Sheridan, Secretary, 1 E. 45th St., New York 17,
- AMERICAN GERIATRICS SOCIETY, Hotel Traymore, Atlantic City, N. J., June 4-5. Dr. Richard J. Kraemer, Secretary, 2907 Post Rd., Warwick, R. I.
- AMERICAN MEDICAL ASSOCIATION, Traymore Hotel, Atlantic City, N. J., June 8-12. Dr. F. J. L. Blasingame, Executive Vice President, 535 N. Dearborn St., Chicago 10, Ill.
- AMERICAN MEDICAL WOMEN'S ASSOCIATION, Sheraton Ritz Carlton Hotel, Atlantic City, N. J., June 4-7. Miss Lillian T. Majally, Executive Secretary, 1790 Broadway, New York 19, N. Y.
- AMERICAN NEUROLOGICAL ASSOCIATION, Claridge Hotel, Atlantic City, N. J., June 15-17. Dr. Charles Rupp, Secretary, 133 S. 36th St., Philadelphia 4, Pa.
- AMERICAN RHEUMATISM ASSOCIATION, Mayflower Hotel, Washington, D. C., June 2-6. Dr. Edward F. Hartung, Secretary, 580 Park Ave., New York
- AMERICAN THERAPEUTIC SOCIETY, Shelburne Hotel, Atlantic City, N. J., June 4-7. Dr. Oscar B. Hunter, Jr., Secretary, 915 19th St., N.W., Washington 6, D. C.
- INTERNATIONAL CARDIOVASCULAR SOCIETY, NORTH AMERICAN CHAPTER, Shelburne Hotel, Atlantic City, N. J., June 6. Dr. Paul T. DeCamp, Secretary, 3503 Prytania St., New Orleans, La.
- SOCIETY FOR INVESTIGATIVE DERMATOLOGY, Ritz Carlton Sheraton Hotel, Atlantic City, N. J., June 6-7. Dr. Herman Beerman, Secretary, 255 S. 17th St., Philadelphia 3, Pa.
- SOCIETY OF BIOLOGICAL PSYCHIATRY, Claridge Hotel, Atlantic City, N. J., June 13-14. Dr. George N. Thompson, Secretary, 2010 Wilshire Blvd., Los Angeles 57, Calif.

August

AMERICAN HOSPITAL ASSOCIATION, Statler Hotel, New York, N. Y., August 24–27. Dr. Edwin L. Crosby, Director and Secretary, 18 E. Division St., Chicago, Ill.

September

AMERICAN ASSOCIATION OF MEDICAL CLINICS, Sheraton-Blackstone Hotel, Chicago, Ill., September 24–26. Dr. Edwin P. Jordan, Executive Secretary, Box 58, Charlottesville, Va.

AMERICAN COLLEGE OF GASTROENTEROLOGY, Biltmore Hotel, Los Angeles, Calif., September 19-26. Mr. Daniel Weiss, Executive Director, 33 W. 60th St., New York 23, N. Y.

AMERICAN SOCIETY OF CLINICAL PATHOLOGISTS, The Palmer House, Chicago, Ill., September 7-11. Mr. Claude E. Wells, Executive Secretary, 2052 N. Orleans, Chicago 14, Ill.

COLLEGE OF AMERICAN PATHOLOGISTS, The Palmer House, Chicago, Ill., September 6. Dr. Arthur H. Dearing, Executive Director, Suite 2115 Prudential Plaza, Chicago 1, Ill.

WORLD MEDICAL ASSOCIATION, Montreal, Canada, September 7-12. Dr. Louis H. Bauer, Secretary-General, 10 Columbus Circle, New York 19, N. Y.

PERSONAL NOTES

Dr. Robert I. Wise, (Associate), Philadelphia, Pa., was recently appointed Magee Professor of Medicine and Head of the Department of Medicine at The Jefferson Medical College of Philadelphia. He succeeds Dr. William A. Sodeman, F.A.C.P., who was named Dean of the College on April 22, 1958. Dr. Wise received his M.D. degree from the University of Texas Medical Branch and a Ph.D. degree in Bacteriology from the University of Illinois College of Medicine.

Dr. Thomas B. Magath, F.A.C.P., Head of the Section of Clinical Pathology, Mayo Clinic, Rochester, Minn., and Professor of Pathology, University of Minnesota (Mayo Foundation), was honored recently at a dinner meeting of the American Society of Clinical Pathologists and College of American Pathologists. He received the Ward Burdick medal for "most meritorious contributions to the science of clinical pathology."

Dr. W. Reece Berryhill, F.A.C.P., Dean of the University of North Carolina School of Medicine, Chapel Hill, N. C., was recently elected Vice President of the Association of American Medical Colleges.

Three members of the College were named "Emeritus" members of the faculty of the Vanderbilt University School of Medicine recently. They included Drs. John B. Youmans, F.A.C.P., Emeritus Dean and Professor of Medicine; Hugh J. Morgan, M.A.C.P., Emeritus Professor of Medicine, and Hollis E. Johnson, (Associate), Emeritus Professor of Clinical Medicine.

Dr. Milford O. Rouse, F.A.C.P., Dallas, Tex., was named President of the Southern Medical Association at the Annual Meeting of the Association held in New Orleans, La., recently.

Three Fellows of the College were guest speakers at the 22nd Annual Meeting of the New Orleans Graduate Medical Assembly, March 2-5, 1959. They were Drs. Otto H. Janton, Philadelphia, Pa., "Cardiology"; Clifford J. Barborka, Chicago, Ill., "Gastroenterology," and William Dameshek, Boston, Mass., "Internal Medicine."

Dr. David A. Rytand, F.A.C.P., was recently named the first Bloomfield Professor of Medicine at the Stanford University School of Medicine, San Francisco, Calif. The professorship honors Dr. Arthur L. Bloomfield, M.A.C.P., San Francisco, Calif., who retired in 1954 as Emeritus Professor of Medicine.

Dr. Philip S. Hench, F.A.C.P., Professor of Medicine, University of Minnesota (Mayo Foundation), Rochester, Minn., discussed the subject, "Pathogenesis and Treatment of Rheumatoid Arthritis," at the first Chicago Postgraduate Course in Arthritis and Related Subjects held February 19–21, 1959. The course was sponsored by the Chicago Rheumatism Society, the Chicago Orthopaedic Society, and the Illinois Chapter of the Arthritis and Rheumatism Foundation.

Dr. Samuel Bellet, F.A.C.P., Professor of Clinical Cardiology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., was a participant at the recent meeting of the Gerontological Society in Philadelphia, Pa.

Dr. Joseph A. Lundy, F.A.C.P., Worcester, Mass., has been named President of the Worcester District Medical Society for 1958-59.

Dr. Carl V. Moore, F.A.C.P., A.C.P. Governor for Missouri, was the eighth annual Physician-in-Chief Pro Tempore at the Cleveland (Ohio) Clinic, December 18-20, 1958.

Dr. John H. Lawrence, F.A.C.P., Director, Donner Laboratory, University of California, Berkeley, Calif., gave several lectures at the opening ceremonies of the Medical School of the University of Bordeaux, France, and received an honorary doctor's degree.

Dr. William D. Paul, F.A.C.P., lowa City, Iowa, was named a member of the Executive Board of the American Institute of Ultrasonics in Medicine at a recent meeting held in Philadelphia, Pa.

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, Pa., discussed the subject, "The Role of Hiatus Hernia in the Differential Diagnosis of Cardiac and Gastrointestinal Affections," at the 43rd International Medical Assembly, Postgraduate Medical Association of North America, in Cleveland, Ohio, November 10, 1958.

Dr. John Zarit, F.A.C.P., Denver, Colo., was named President, and Dr. William C. Service, F.A.C.P., Colorado Springs, Colo., was elected Treasurer, of the Colorado State Medical Society at a recent meeting of the Society.

Dr. Arnold S. Relman, (Associate), Associate Professor of Medicine, Boston University School of Medicine, Boston, Mass., directed a series of conferences, ward

rounds, and clinics, concerning "Electrolyte Problems and Renal Disease" which were sponsored by the Milwaukee Academy of Medicine, December 16-20, 1958.

Two Fellows of the College who are faculty members of the Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C., were recently named to special committees. Dr. Harold D. Green, Professor of Physiology and Pharmacology, will serve on the Postdoctoral Fellowship Committee of the National Science Foundation, and Dr. Wingate M. Johnson, Professor of Clinical Medicine, is a member of the Committee on Aging of the American Medical Association and has been recently appointed to the North Carolina Governor's Coordinating Committee on Aging.

Dr. Frank P. Foster, F.A.C.P., Boston, Mass., was a member of the panel which discussed "Arthritis" at the Lahey Clinic Fellowship Lectures held January 14, 1959, in Boston, Mass.

Dr. Philip Reichert, F.A.C.P., has been appointed Executive Director of the American College of Cardiology, with headquarters in New York City.

Dr. Nathaniel G. Berk, F.A.C.P., Philadelphia, Pa., was a speaker at the Symposium on the Therapeutic Aspects of Nutrition at a meeting of the Bronx Chapter of the American College of Surgeons at New York, N. Y., December 4, 1958.

Dr. Edwin E. Osgood, F.A.C.P., Professor of Medicine and Head of the Division of Experimental Medicine at the University of Oregon Medical School, Portland, Ore., was Chairman of the Symposium on Blood and Blood-Forming Cell Cultures, and delivered a paper at the 7th Congress of the International Society of Hematology in Rome, Italy, during September 1958.

Dr. Charles M. Caravati, F.A.C.P., Professor of Clinical Medicine, Medical College of Virginia, Richmond, discussed the subject, "An Appraisal of Present Therapy for Peptic Ulcer," at the 10th Anniversary Meeting of the West Virginia Chapter of the American Academy of General Practice held in Charleston, W. Va., December 7, 1958.

Dr. Henry T. Friedman, (Associate), Assistant Clinical Professor of Medicine (Allergy), University of California School of Medicine at Los Angeles, was Chairman, and Drs. John M. Sheldon, F.A.C.P., Ann Arbor, Mich., and William B. Sherman, F.A.C.P., New York, N. Y., were guest speakers at a postgraduate course on Allergies sponsored by the University Extension and the University of California School of Medicine at Los Angeles, January 23–24, 1959.

Dr. Robert S. Dow, F.A.C.P.; Associate Clinical Professor of Medicine (Neurology), University of Oregon Medical School, Portland, Ore., and Dr. Giuseppe Moruzzi, Pisa, Italy, are co-authors of a new text, "The Physiology and Pathology of the Cerebellum." Published by the University of Minnesota Press, the book was made possible by a Fulbright Research Scholarship awarded Dr. Dow in 1953.

Dr. Laurence Selling, F.A.C.P., Emeritus Professor of Medicine, University of Oregon Medical School, Portland, Ore., received the following citation at Charter Day ceremonies on October 22, 1958: "Laurence Selling, native son, was educated at Yale and The Johns Hopkins University School of Medicine. After postgraduate work in Germany, he returned to Oregon to practice, and immediately entered upon a distinguished teaching career with the University of Oregon Medical School where he earned the lasting devotion of his students and his colleagues. Throughout his career, Dr. Selling has had an abiding interest in research. Symbolic of that interest and his achievements are the Laurence Selling Student Research Scholarships which have been endowed to stimulate interest in research among the students in the Medical School. In addition to serving education through his own profession, Dr. Selling has found time and energy to advance the general cause of learning. Of him, his colleagues have written, 'We have known and now know many great physicians. Dr. Selling is one of the greatest.'"

During a recent month's tour as National Consultant in Internal Medicine to the "United States Air Force Medical Installation" in England, Germany and France, Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, Pa., addressed the USAFE Medical-Surgical Conference at Wiesbaden, Germany, on "Recent Advances in the Management of Diabetes" and the West Germany Armed Forces Medical Society at Ramstein, Germany, on "Diabetes." Other addresses dealt with "Management of Essential Hypertension," "Spontaneous Hypoglycemia," "Thyrotoxicosis," and "Practical Considerations of Nutrition in Medical Practice."

Dr. Leslie H. French, F.A.C.P., Associate Professor of Clinical Medicine, Georgetown University School of Medicine, Washington, D. C., is presenting a course in "Electrocardiography and Vectorcardiography" at the Heart Station of the Prince George's General Hospital, Cheverly, Md. The course started on Friday, December 18, and will continue for 18 weeks.

Dr. George C. Griffith, F.A.C.P., Professor of Medicine at the University of Southern California School of Medicine, Los Angeles, Calif., and President of the Los Angeles County Heart Association, and Dr. Sim P. Dimitroff, F.A.C.P., Assistant Clinical Professor of Medicine, University of Southern California School of Medicine, and Chairman of the Cardiac Clinics Committee of the Heart Association, announced the publication of a Cardiac Clinic Directory evaluating 24 clinics in the Los Angeles County Area. The Directory is a result of a nine-year effort of the Heart Association to encourage the improvement of existing facilities and the establishment of more cardiac clinics.

Four Fellows of the College from the State of Texas were elected officers of the Texas Academy of Internal Medicine at a recent meeting. Included were: Drs. Merton M. Minter, San Antonio, President; Robert H. Mitchell, Plainview, President-Elect; Abbe A. Ledbetter, Houston, Vice President, and Hugo T. Engelhardt, Sr., Houston, Secretary-Treasurer.

Colonel Frank M. Townsend, F.A.C.P., U.S. Air Force (M.C.), Deputy Director of the Armed Forces Institute of Pathology and former Chairman of the Joint Committee of Aviation Pathology, comprised of representatives of the United States, Great Britain and Canada, was recently elected to Direct Fellowship in the American College of Physicians.

Dr. George J. Train, F.A.C.P., Brooklyn, N. Y., was co-author of a paper entitled "Acts of Violence Associated with Electroencephalographic Changes," which was presented at the Regional Meeting of the American Psychiatric Association at Miami Beach, Fla., December 2, 1958.

Dr. Charles Watkins, (Associate), Professor of Psychiatry and Head of the Department of Psychiatry and Neurology at the Louisiana State University School of Medicine, New Orleans, La., was elected Vice President of the Southern Psychiatric Association at its recent annual meeting. He is also President of the New Orleans Society of Neurology and Psychiatry.

Dr. Henry J. Tagnon, F.A.C.P., Brussels, Belgium, has been appointed Clinical Director of the Institut Jules Bordet, University of Brussels Cancer Center. Dr. Tagnon is also Chief of the Department of Medicine and Clinical Investigation of the Institut.

Dr. Edmund Jacobson, F.A.C.P., Chicago, Ill., discussed the subject, "Electrical Measurements of Mental Activities," and "Physiological Psychiatry: Diagnostic, Clinical and Research Principles for a Science of Neuropsychiatry Implemented by Electroencephalography," at the Municipal University of Wichita, Kans., on November 21, 1958. He also served as a Consultant for a research project being conducted at the University under a grant from the National Institute of Mental Health.

Dr. Pierre C. Simonart, F.A.C.P., Philadelphia, Pa., discussed the subject, "Allergy and Conditioning," at the Annual Convention of the American Academy of Dermatology and Syphilology held December 8–10, 1958.

Three Fellows of the College from California presented papers at the 5th International Congress on Diseases of the Chest sponsored by the American College of Chest Physicians Council on International Affairs and held in Tokyo, Japan, September 7–11, 1958. Included were: Drs. Seymour L. Cole, Beverly Hills, "Therapy of Angina Pectoris: Evaluation of Antianginal Agents and Procedures"; Edward C. Rosenow, Jr., Los Angeles, "The Diagnosis of Coronary Artery Disease, Especially Angina Pectoris," and Samuel A. Weisman, Los Angeles, "Radiological Evaluation of the Heart Size."

Dr. William B. Bean, F.A.C.P., Professor and Head of Department of Internal Medicine at the State University of Iowa College of Medicine, Iowa City, Iowa, has been named Chairman of the Scientific Assembly of the American Medical Association Section on Internal Medicine for the 1959 meeting to be held in Atlantic City, N. J.

Three members of the College were recently named officers of the State Societies of the American Society of Internal Medicine. Included were: Drs. Monroe T. Gilmour, F.A.C.P., Charlotte, President, North Carolina Society of Internal Medicine; Roy S. Bigham, Jr., F.A.C.P., Charlotte, Secretary-Treasurer, North Carolina Society of Internal Medicine, and Richard N. O'Dell, (Associate), Charleston, Secretary-Treasurer, West Virginia Society of Internal Medicine.

Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., was elected Minnesota Vice President of the Mississippi Valley Medical Society at the 23rd Annual Meeting of the Society in Chicago, Ill., December 1, 1958.

Dr. T. Joseph Reeves, (Associate), Birmingham, Ala., recently completed a year's study at the Queen Elizabeth Hospital, Birmingham University School of Medicine, Birmingham, England, and returned to his position as Associate Professor of Medicine, in the Department of Medicine at the Medical College of Alabama.

New Carrier for the College Sponsored Professional Liability Plan

As of January 1, 1959, the Liberty Mutual Insurance Company, of Boston, became the carrier of the Professional Liability Plan sponsored by the College. The new carrier was chosen only after a nationwide survey and study had been made to obtain an American carrier who was licensed in all states, Puerto Rico, Hawaii and Canada. The Liberty Mutual fulfills the standards and objectives of the College. It is the largest mutual casualty company in the world with assets of \$534,000,000.00. The Liberty Mutual has 149 branch offices throughout the United States alone. The rates charged under the new plan are 10% below the so-called National Bureau of Casualty Underwriters' rates in all states except Louisiana. Furthermore, Liberty Mutual has returned \$455.5 millions to policyholders as dividend savings. The most recent dividend on Professional Liability Insurance was 15%.

Complete information on this new plan should be in the hands of all College members prior to this issue of the Annals. Briefly, coverage is available for \$10/30,000, \$25/75,000, \$50/150,000, \$100/300,000, and \$200/600,000 limits. Protection is also available for partnerships and for the acts of employed technicians as well as coverage for x-ray and shock therapy.

A brief description of the coverage follows:

The policy provides insurance for:

- (1) Payment of such sums as the insured may become legally obligated to pay as damages because of injury, sickness, disease or death caused by
 - (a) malpractice, error or mistake in rendering or failing to render professional services in the practice of insured's profession;
 - (b) malpractice, error or mistake committed by any person for whose acts or omissions the insured is legally responsible;
- (2) Liability of the insured arising out of acts or omissions of any licensed and qualified physician acting as a temporary substitute for the insured;
- (3) Liability of the insured as a member of a partnership.

The policy does not provide insurance for:

- (1) Injury arising out of the performance of a criminal act by any person.
- (2) Injury caused by any person while under the influence of intoxicants or narcotics.

NOTE: The policy does provide for defense for the insured for such claims or suits [(both (1) and (2) above] unless the insured or another person for whose acts or omissions the insured is alleged to be legally responsible is convicted in a criminal prosecution based on those acts or omissions for which claim or suit is brought against the insured.

(3) Liability of others imposed upon the insured person by reason of any contract.

- (4) Liability of the insured under any guarantee or warranty in respect to the diagnosis or treatment of or operation on any person. NOTE: The policy does provide for defense of any suit which alleges such liability [(3) and (4) above] and in which the insured denies the existence of the alleged contract, guarantee or warranty.
- (5) Liability of the insured as proprietor, superintendent or executive officer of any hospital, sanitorium, clinic with bed and board facilities, laboratory or business enterprise.

The policy also provides insurance:

- (1) for the defense of any suit against the insured alleging such injury, sickness, disease or death even if any of the allegations of the suit are groundless, false or fraudulent:
- (2) for payment of premium on release of attachment bonds and appeal bonds;
- (3) for reimbursement of the insured for all reasonable expenses, other than loss of income or earnings, incurred at the company's request;
- (4) settlement, with the written consent of the insured, of any claim or suit as the company deems expedient.

All correspondence and inquiries should be sent to Group Insurance Administrators, 404 South 42nd Street, Philadelphia 4, Pa.

OBITUARIES

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. Patterson Morris Menlowe, (Associate), McKeesport, Pa., December 18, 1958 Dr. Edward Adam Strecker, F.A.C.P., Philadelphia, Pa., January 2, 1959

DR. JAMES HARVEY BLACK

Dr. James Harvey Black, F.A.C.P., of Dallas, Texas, died in that city November 30, 1958, of acute myocardial infarction. He was born in Huntington, West Virginia, March 27, 1884.

He received his preliminary education in the public schools of Paris, Texas, and Southwestern University of Georgetown, Texas. He attended the College of Physicians and Surgeons of Atlanta, Georgia, 1903–1905 and Southern Methodist University Medical Department, 1905–1907, from which he received an M.D. degree. Upon completion of an internship at the St. Paul Hospital, Dallas, he established himself in the practice of Clinical Pathology in Dallas and continued in this practice until 1932. From 1932 until his death he limited his practice to Allergy. He pursued postgraduate education at: Montreal General Hospital, 1912; Research Laboratory, New York Board of Health, 1917; University of Pennsylvania School of Medicine, 1919, and Philadelphia General Hospital, 1920.

His appointments included: Professor of Clinical Medicine, Baylor University College of Medicine, 1915–1943; Professor of Clinical Medicine, University of Texas Southwestern Medical School, 1943–1953; Consultant in Medicine, University of Texas Southwestern Medical School since 1953; Consultant in Pathology, Childrens Medical Center, Dallas, since 1930; Consultant in Allergy, Parkland Hospital, Dallas, since 1945.

Dr. Black contributed extensively to the medical literature on the subjects of clinical pathology, immunology and allergy, with a total of seventy medical papers in addition to co-authorship (with Dr. W. T. Vaughan) of two books entitled "The Practice of Allergy" and "The Primer of Allergy."

Dr. Black was a member of the American Medical Association, the Dallas County Medical Society, the Texas Medical Association, the Southern Medical Association, the Texas Academy of Internal Medicine, the Southwest Allergy Forum, the Texas Society of Pathologists (President in 1934), the American Society of Clinical Pathologists (President in 1929), the American Academy of Allergy, the American Association for the Study of Allergy (Secretary in 1941), the New York Academy of Sciences and the Texas Philosophical Society. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians since 1935.

Dr. Black was highly revered as a scholarly physician, and will be long remembered for his participation in civic and religious affairs of his community. He is survived by his widow, Mrs. Alleen Patton Black, 3624 Princeton Avenue, Dallas 5, Texas.

VICTOR E. SCHULZE, M.D., F.A.C.P., Governor for Texas

DR. JOHN SEBASTIAN DERR

Dr. John S. Derr, F.A.C.P., died in Frederick, Maryland, on October 23, 1958, of a coronary thrombosis, at the age of seventy-seven. Dr. Derr was born in Norfolk, Virginia, on January 6, 1881, and after attending the Jones University School in Charlottesville, Virginia, he entered the University of Virginia Department of Medicine, receiving his M.D. degree in 1905. For a year after graduation he was a member of the Department of Anatomy at the University of Virginia Medical School.

From 1906 to 1908 he served as a Medical Missionary to Nigeria in British West Africa. Returning to the United States in 1908, he interned for two years at the House of the Good Samaritan in Boston. His interest in radiology began during the period of his training in Boston. After an Assistantship in the X-ray Department at The Johns Hopkins Hospital in Baltimore, he entered private practice as a Roentgenologist in Atlanta, Georgia, and practiced there from 1911 to 1926. In Atlanta he was a Member of the Staff of the Georgia Baptist Hospital and the Grady Hospital. In 1926 he moved to Frederick, Maryland, and spent the remainder of his life there.

Dr. Derr's practice was interrupted by World War I, and he served overseas as Roentgenologist at the Base Hospital No. 3, being discharged with the rank of Major in 1919. He maintained an active interest in the Francis Scott Key Post No. 11 of the American Legion and was a Past President of the Sons of the American Revolution and a member of John R. Webb Post No. 1385 of the Veterans of Foreign Wars.

Dr. Derr became a Fellow of The American College of Physicians in 1923. He was also a member of The American Medical Association, the Southern Medical Society, the American Roentgen Ray Society, the American College of Radiology, the Radiology Society of North America, the Medical and Chirurgical Faculty of the State of Maryland, the Frederick County Medical Society, and was a Diplomate of the American Board of Radiology.

Dr. Derr is survived by his wife, Mrs. Jean Rose Derr, of 35 E. Church Street, Frederick, Maryland, and his children, Mrs. Julia Lantham Derr Young of Florida, Mrs. Jeanette Garland Derr Jullien of Arlington, Virginia, and John Sebastian Derr, Jr., of Frederick.

R. CARMICHAEL TILGHMAN, M.D., F.A.C.P., Governor for Maryland

DR. JOSEPH WILLIAM McMEANS

Dr. Joseph William McMeans, F.A.C.P., of Anderson, South Carolina, died in that city September 2, 1958. He was born in Cleveland, Ohio, January 25, 1891.

He received his medical degree from the University of Pittsburgh School of Medicine in 1912, and then interned at the Mercy Hospital, Pittsburgh. He further pursued his medical studies at Columbia University. He also had the following postgraduate training: electrocardiography, Michael Reese Hospital, 1944; cardiovascular disease, Peter Bent Brigham Hospital, 1945; general medicine, The Jefferson Medical College of Philadelphia, 1946; internal medicine, Western Reserve University School of Medicine, 1946, and electrocardiography, University of Michigan Hospital, 1945.

Among his medical appointments were: Assistant Professor of Bacteriology and Immunology, University of Pittsburgh School of Medicine, 1913–24; Allegheny Valley Hospital, 1941–46; McLeod Infirmary, 1947–53; and Pathologist, Anderson County Memorial Hospital, 1953–58. He was largely responsible for developing the blood bank program and expanding the hospital's laboratory facilities, including the School for Laboratory Technicians.

Dr. McMeans was a member of the following organizations: the American Medical Association; the American Association of Pathologists and Bacteriologists; Society for Experimental Biology and Medicine; Fellow, American Society of Clinical Pathologists; College of American Pathologists (Founding Fellow); the American Society for Study of Neoplastic Diseases; Florence County Medical Society; Pee Dee Medical Society; the South Carolina Medical Association. He was a Diplomate of the American Board of Pathology and became a Fellow of the American College of Physicians and a Life Member in 1950. He was a Shriner and a member of Alpha Omega Alpha.

Dr. McMeans wrote extensively, and many articles appeared in the medical literature. He was admired and held in highest respect by his colleagues and the community.

He is survived by his wife, Mrs. Erma Williams McMeans, Brown Road, R.F.D. #1, Anderson, South Carolina.

O. B. MAYER, M.D., F.A.C.P., Governor for South Carolina

DR. HARRY DICKEY SEWELL

Dr. Harry Dickey Sewell, F.A.C.P., died in Wellesley Hills, Massachusetts, on August 25, 1958. Dr. Sewell was born in Mansfield, Ohio, on March 18, 1883. He received a B.S. degree from the University of Pennsylvania in 1906 and an M.D. degree from the University of Pennsylvania School of Medicine in 1909. He interned at the Episcopal Hospital in Philadelphia, 1910 to 1912, and took postgraduate training in dermatology and syphilology at the University of Minnesota School of Medicine during periods of 1922, 1929, and 1941. In 1942 he took special training in internal medicine at the Mayo Clinic at Rochester, Minnesota.

Dr. Sewell practiced medicine in Huron, South Dakota, and was a staff member of the Huron Clinic and the Sprague Hospital from 1920 to 1939. He was a Physician in Industrial Medicine on the staff of the Eastman Kodak Company, Rochester, New York, from 1943 to 1946. From 1947 until his retirement, he served as Senior Medical Officer of the Veterans Administration Out-Patient Clinic in Rochester, New York. He was held in high esteem by the staff of the Clinic as well as by the community physicians with whom he was associated.

During the First World War, he was a member of the Medical Corps of the United States Army with the rank of Captain, and served at Camp Fremont, California, from 1918 to 1919.

Dr. Sewell was a member of the American Medical Association; the American Academy of Dermatology and Syphilology; the Rochester Academy of Medicine, and the Monroe County Medical Society (New York). He became a Fellow of the American College of Physicians in 1940.

Dr. Sewell is survived by his wife, Mrs. Mary K. Sewell, who resides at 19 Cunningham Road, Wellesley Hills, Massachusetts.

DR. GLADYS RICHARDA WILLIAMSON

Dr. G. Richarda Williamson, F.A.C.P., was born May 1, 1891, in Cheshire, England, and died in New Orleans, Louisiana, on September 19, 1958. She was the daughter of Richard and Elizabeth Bagbie-Browne Williamson. She graduated from Trinity College, Dublin, in 1910, then deceived the degrees of M.S. and CH.B. in 1916 from the University of Edinburgh and the degree D.P.H. from Glasgow University in 1919. From this time until she came to New Orleans in 1920 she served as a Medical Officer at Baregour Hospital in Midlothian, Scotland.

She became associated with the Tulane University School of Medicine in 1920 shortly after her arrival in the United States, and served successively as Clinical Assistant in Pediatrics, Instructor, Assistant Professor and Professor; on her retirement in 1956 she became an Emeritus Professor. Dr. Williamson was an Associate Visiting Physician in Pediatrics at the Charity Hospital since 1920; Senior Pediatrician of the Child Welfare Association since 1921; Senior Visiting Pediatrician at the Southern Baptist Hospital since 1925; Pediatrician of the Sarah Mayo Hospital since 1921.

She was a Fellow of the American Academy of Pediatrics and of the American College of Physicians (Fellow, 1928; Life Member, 1955); also a member of the British Medical Association, the American Medical Association, the Louisiana State Medical Society and the Orleans Parish Medical Society.

She published a number of articles relative to pediatrics which appeared in leading medical journals in the United States and England.

M. D. HARGROVE, M.D., F.A.C.P., Governor for Louisiana

DR. EMANUEL YADKOWSKY

Dr. Emanuel Yadkowsky, (Associate), of Maplewood, New Jersey, died of a heart attack on August 23, 1958. Born in Newark, he moved to Maplewood five years ago. He was a graduate of Bellevue Hospital Medical School, New York, in 1903.

He was Chief of the Allergy Clinic at Beth Israel Hospital and a Newark physician for 55 years. A member of the original staff of Beth Israel, Dr. Yadkowsky was its first Pathologist and formerly served as Chief Pathologist.

Dr. Yadkowsky was a member of Composite Lodge F and AM; B'nai B'rith; Foresters Association of America; the Essex County Medical Society and the American Medical Association. He had been an Associate of the American College of Physicians since 1925.

Dr. Yadkowsky is survived by his wife, Mrs. Elizabeth L. Yadkowsky, 5 Brookside Road, Maplewood, New Jersey; a daughter, Mrs. Dolores Dakelman of West Orange; a brother, Abraham, of Savannah, Georgia, and a grandchild. The College extends deep sympathy to the bereaved family.

EDWARD C. KLEIN, JR., M.D., F.A.C.P., Governor for New Jersey



Regularity and Metamucil

Both are basic for relief and correction of constipation

Effective relief and correction of constipation require more than clearing the bowel. Basic to the actual correction of the condition itself is the establishment of regular bowel habits. Equally basic is Metamucil which adds a soft, inert bulk to the bowel contents to stimulate normal peristalsis and also to retain water within stools to keep them soft and easy to pass. Thus Metamucil induces natural elimination and promotes regularity.

Metamucil[°]

brand of psyllium hydrophilic mucilloid

SEARLE

WANTED

Back Issues of

ANNALS OF INTERNAL MEDICINE

Good used copies of the following issues are now needed. Only those issues which are currently being advertised will be accepted.

\$1.50 each for

| Vol. | 1. No. | 1-July, 1927 | Vol. 3, N | io. 2-August, 1929 |
|------|--------|------------------|-----------|------------------------|
| Vol. | 1, No. | 2 -August, 1927 | Vol. 3, N | io. 3 -September, 1929 |
| Vol. | 1, No. | 4-October, 1927 | Vol. 3, N | lo. 4-October, 1929 |
| Vol. | 1, No. | 7-January, 1928 | Vol. 3, N | lo. 5-November, 1929 |
| Vol. | 2, No. | 5-November, 1928 | Vol. 3, N | lo. 6-December, 1929 |
| Vol. | 3. No. | 1-July, 1929 | Vol. 5, N | lo. 12 -June, 1932 |

\$1.00 each for

| Vol. | 6, No. 4 -October, | | | 8-February, 193 | 3 |
|------|--------------------|---------|-------------------|-----------------|---|
| | 1 | Vol. 6. | No. 9 March, 1933 | | |

75¢ each for

| Vol. 18, No. | 4 -April, 1943 | Vol. 48, No. 2 — February, 1958 |
|--------------|-------------------|---------------------------------|
| Vol. 24, No. | 1 - January, 1946 | Vol. 48, No. 5 - May, 1958 |
| Vol. 46, No. | 2-February, 1957 | Vol. 49, No. 3-September, 1958 |
| | Vol. 49. | No. 4 - October, 1958 |

Address Journals to:

| E. R. | LOVELAND. | Executive | Secretary |
|-------|-----------|-----------|-----------|

4200 Pine Street, Philadelphia 4, Pa.



DIASAL

doubly valuable for patients on salt-restricted diets

Besides encouraging the patient's adherence to diet, DIASAL offers pleasant-tasting prophylaxis against the potassium loss incurred by the use of the more recent oral diuretics. The potassium supplementation, concurrently supplied by DIASAL, helps avoid digitalis toxicity due to urinary loss of this ion. Constituents: Potassium chloride, glutamic acid and inert excipients. Available in 2-ounce shakers and 8-ounce bottles.

POLICERA

E. FOUGERA & CO., INC., Hicksville, Long Island, New York

4595



Preparation for BMR test takes but a few moments. Three dials are set. Patient is connected to system. Compressed oxygen is automatically released and timer starts. When test is completed, button is pressed and BM rate is read.

Give basal metabolism tests the quick, easy, reliable way...with a modern, self-calculating L-F BasalMeteR.

Ritter

GOMPANY, DE.

ROCHESTER, NEW YORK

Medical-Hospital Division

| RITTER COMPANY, IN | C. | | |
|-----------------------------|----|----|----|
| Medical-Hospital Division | on | | |
| 6351 Ritter Park, Rochester | 3, | N. | Y. |

Send me literature on the BasalMeteR-BMR testing the modern way!

Name.....

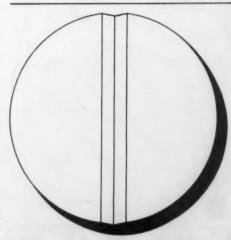
Address.....

City..... State......

COUNTRIBUCE

DOUBLE POTENCY

AT LOW COST TO YOUR PATIENT



Pentids 400

For the treatment of penicillin susceptible infectionsranging from mild to moderately severe-due to hemolytic streptococcus / pneumococcus / staphylococcus / and for the prevention of streptococcal infections where there is a history of rheumatic fever

Clinical effectiveness confirmed by millions of cases Specific in many common infections Daily dosage may be spaced without regard to mealtime Ease of administration with oral penicillin Economy for the patient

SQUIBB



Squibb Quality- the Priceless Ingredient

new convenient oral tablets

PENTIDS '400,' each scored tablet con-tains 400,000 units of penicillin G potas-sium buffered, bottles of 12 and 100. Twice the unitage of Pentids 200,000 units

PENTIDS, 200,000 units of buffered penicillin G potassium per scored tablet, bottles of 12, 1 and 500.

PENTIDS FOR SYRUP, 200,000 units of penicillin G potassium per tenspoonful (5 cc.), 12 dess PENTIDS, CAPSULES, 200,000 units of penicillin G potassium per capsule, bottles of 24, 160, and

PENTIDS SOLUBLE TABLETS, 200,000 units of penicillin G potassium per tablet, visits of 12 and

PENTIDS-SULFAS TABLETS, 200,000 units of penicillin G potassium with 0.5 Gm. triple suifes penaltiples. Bottles of 30, 100, and 500.

SENTIDAD IS A SQUISS TRADERA



For more certain control of virtually ALL

DIARRHEAS

PIONNAGED

ANTIBIOTIC . ADSORBENT . DEMULCENT . ANTISPASMODIC

Diarrheas due to neonyeln-sus public pathogens are effectively treated by the highly efficient intestinal antibiotic in DONNAGEL WITH NEOMYCIN, whose other ingredients serve to control toxic arbitative and emotional sous. Result Early resetablishment of normal bowel function.

SUPPLY: Bottles of 6 fl. oz.

ALSO AVAILABLE DON'S MEET the real and formula for use when the antibiotic component is not unlicated. Bottles of 6 ff. oz.

each 30 cc (1 fl oz.) of the comprehensive formula of DONNAGEL WITH NEOMYCIN contains:

| Neomycin sulfate | 300 mg. |
|------------------------|------------|
| | 6.0 Gm |
| Pectin (2 gr.) | 142.8 mg |
| | |
| | |
| Atropine sulfate | _0.0194 mg |
| Hyoscine hydrobromide | |
| Phenobarbital (14 gr.) | 16.2 mg |
| | |

because an accurate diagnosis depends on an accurate record...

more and more doctors are using the BURDICK EK-III ELECTROCARDIOGRAPH

DUAL-SPEED ELECTROCARDIOGRAPHY AT ITS FINEST

For complete specifications and information on the EK-III, please write directly to: The Burdick Corporation, Milton, Wisconsin or call your local Burdick representative.



THE BURDICK CORPORATION
MILTON, WISCONSIN
Branch Offices:
NEW YORK • CHICAGO • ATLANTA • LOS ANGELES
Dealers in all principal cities /



for everyday pain control . . .

for your many patients requiring potent analgesia but not an injected narcotic

Proved by extensive evaluation^{1,2,3} in 1998 patients in diverse areas of medicine and surgery, including: arthritis, bursitis, early metastatic carcinoma, fibrositis, grippe, herpes zoster, ligamental strain, low back pain, menstrual pain, myalgia, myositis, neuritis, pleurisy, postoperative pain, postpartum pain, sciatica, trauma, dental pain

- exclusive Wyeth non-narcotic analgesic plus anti-inflammatory action
- prompt, potent action—as potent as codeine
- documented effectiveness and safety1,2,3

Supplied: Tablets, bottles of 48. Each tablet contains 75 mg. of ethoheptazine citrate and 325 mg. (5 grains) of acetylsalicylic acid. Philadelphia 1, Pa.



Cass, L.J., et al., J.A.M.A. 166:1829 (April 22) 1958.
 Batterman, R.G., et al., Am. J. M. Sc. 224:413 (Oct.) 1957.
 Medical Department. Wyeth: Final Report on the Cilinical Evaluation of Zactirin.



ELES



Since hypocalcemic tetany-usually the result of parathyroid deficiency-may require treatment for years, effective oral therapy with Hytakerol is superior to other methods.

Hytakerol increases absorption of calcium from the intestine and can be taken with undiminished effectiveness, indefinitely.

For prophylaxis following thyroidectomy and for chronic hypoparathyroidism, "... dihydrotachysterol... has proved to be the most valuable remedy ... "1

"Dihydrotachysterol ... is of great therapeutic value in most cases of both normocalcemic and hypocalcemic tetany."2

inthrop LABORATORIES NEW YORK 18, N. Y.

- Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
- Sandock, Isadore: Tetany and ovarian function. J.A.M.A., 160:659, Feb. 25, 1956.

Hytakerol, trademark reg. U.S. Pat. Off.

DOSAGE: Orally from 3 to 10 cc. (or from 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose from 1 to 7 cc. (or from 2 to 14 capsules) depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate should be given daily as supplement through the period of therapy.

SUPPLIED: Hytakerol in Oil, bottles of

Hytakerol Capsules (each equivalent to 0.5 ec.), bottles of 50.

Chrostek's Sign— Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen —one of the diagnostic indications of hypocalcemic tetany





OVERWHELMING SYSTEMIC INFECTION-in certain fulminaling infections, when the patient's life is in danger, INJECTION HYDELTRASOL can be a lifesaving measure until sufficient time elapses for specific antibiotic therapy

DISABLED ARTHRITIC-INJECTION HYDELTRASOL provides strikingly prempt relief from pain, discomfort and disability—may be administered with HYDEURA-T.B.A. for prompt onset of action and prolonged duration of relief [CYCLRINE* (Hexylkaine Hydrochlonde) may be used initially to locate trigger points before injection].



In your bag... ready for use ... IMMEDIATELY!

THE FIRST READY-TO-USE, SOLUBLE, ALL-PURPOSE PARENTERAL STEROID

INJECTION HYDELTRAS

ADVANTAGES:

- 1. Immediately effective-dramatic response in minutes
- 2. Ready for use-needs no reconstitution or refrigeration
- 3. In solution—flows readily through a small-bore needle

SUPPLIED: In 2-cc. and 5-cc. vials, each cc. containing 20 mg. of prednisolone 21-phosphate as the di-sodium salt. Hydeltrasol is a trademark of Morck & Co., Inc.

MERCK SHARP & DOHME DIVISION OF MERCK & CO., INC., Philadelphia 1, Pa.



WHEN BLOOD PRESSURE MUST COME DOWN...



When hypertensive symptoms such as dizziness, headache and fainting are frequent enough and severe enough to interfere with your patient's activity and safety—then it is time to consider the beneficial actions of Serpasil-Apresoline. Both Serpasil and Apresoline lower blood pressure. When the Serpasil-Apresoline combination tablet is prescribed, blood pressure response is even better. In addition, Serpasil contributes favorable calming and heartslowing effects. Apresoline increases renal blood

flow, decreases cerebral vascular resistance and inhibits the actions of humoral pressor agents. Combined with Serpasil, Apresoline is effective at a lower dosage, thus side effects are rarely a serious problem.

**SUPPLIED:* Tablets #4 (standard-strength), each containing 0.2 mg. of Apresoline. Tablets #1 (half-strength), each containing.

Serpasif-Apresoline

hydrochloride (reserpine and hydralazine hydrochloride CBA)

2/2000 MI

OF IT IT A SUMMET, NEW JERSE

now, for the first time, liquid meprobamate



Suspension



acceptably flavored . . .

your answer to tablet problems in anxiety and tension states

- in children
- · in the aged
- in all patients who reject tablet medication

SUPPLIED: Suspension, 200 mg. per 5-cc. teaspoonful, bottles of 4 fluidounces. Also available: Tablets, 400 mg., scored, bottles of 50; 200 mg., scored, vials of 50. WYSEALS® EQUANIL, tablets, 400 mg., vials of 50.

RELIEVES TENSION-MENTAL AND MUSCULAR



Conforms to Code

for all your patients starting on corticoids

Kenacort safely starts your patients off right - with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased antiallergic, antirheumatic or anti-inflammatory activity is provided on a low dosage schedule.1-3 Clinical improvement is accomplished without water or salt retention,1-4 or adverse effect on blood pressure.1-3,5 A low sodium diet is not necessary.4.5 Gastrointestinal disturbances are negligible^{2,4,5} with less chance of peptic ulcer.4 and there is no psychic stimulation to distort the clinical response.1-3 This makes Kenacort particularly valuable in treating your "problem patients" - such as the obese or hypertensive and the emotionally disturbed.

- nerental:
 1. Freyberg, R.H.: Berntsen, C.A., Jr., and Hellman, L.: Arth. & Rheum. 1:215 (June) 1958.
 2. Sherwood, H., and Cooke, R.A.: J. Allergy 28:97 (March) 1957.
 3. Shelley, W.B.; Harun, J.S., and Pilisbury, O.M.: J.A.M.A. 187:959 (June 21) 1958.
 4. Dubois, E.L.: California Med. 88:195 (Sept.) 1958.
 5. Hartung, E.F.: J.A.M.A. 187:973 (June 21) 1958.

SQUIBB



Squib Triancinolone

for all your arthritic patients requiring corticoids

Kenacort, particularly in the treatment of your arthritic patients, has proved effective where other steroids have failed. It provides prompt, safe relief of pain, stiffness and swelling - and may even forestall crippling deformities if started soon enough. Rapid clinical improvement is obtained on a low dosage schedule1-3 with few side effects to worry about.1-5 (Kenacort is particularly valuable for your arthritic patients with hypertension, cardiac disease, obesity 'and those prone to psychic disturbances.) And clinical evidence has shown that Kenacort suppresses the rheumatic process.1,5 Because of its relative freedom from untoward reactions, it provides corticosteroid benefits to many patients who until now have been difficult to control. Kenacort, too, offers the same benefits when treating allergies, dermatoses, and asthma.

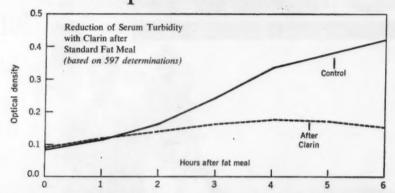
SUPPLIED

Scored tablets of 1 mg. — Bottles of 50 Scored tablets of 2 mg. — Bottles of 50 Scored tablets of 4 mg. — Bottles of 30 and 100

in the management of atherosclerosis

Clarin * (sublingual heparin potassium, Leeming)

clears lipemic serum



Each time your patients eat a substantial fat-containing meal, lipemia results. Small amounts of injected heparin will help control this increased fat content in the blood, 1.2 but widespread adoption of this method has been hampered by its inconvenience, pain, cost and the necessity for periodic checks on blood clotting time.

Now, long-term preventive heparin therapy is practical for the first time with the introduction of CLARIN—which is heparin in sublingual form. Each CLARIN tablet contains 1500 I.U. of heparin potassium—a sufficient amount to clear lipemic serum without affecting coagulation mechanisms.^{3,4}

With one mint-flavored CLARIN tablet under the tongue after each meal, lipemia is regularly controlled, removing a constant source of danger to the atherosclerotic patient. He may eat safely, with less fear of dangerous results, without hard-to-follow diets.

The varied implications of CLARIN in beneficially affecting fat metabolism are obviously far-reaching. The relationship between heparin, lipid metabolism and atherosclerosis

may well be analogous to that between insulin, carbohydrate metabolism and diabetes mellitus.⁵

Use CLARIN to protect your atherosclerotic patients—the postcoronaries and those with early signs of coronary artery disease.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.

Council on Drugs, J.A.M.A. 166:52 (Jan. 4) 1958.
 Hahn, P. F.: Science 98:19 (July 2) 1943.
 Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
 Rubio, F. A., Jr.: Personal communication.
 Engelberg, H., et al.: Circulation 13:489 (April) 1956.

*Trade Mark. Patent applied for.

Thos. Leeming & Co., Inc.

155 East 44th Street, New York 17, N. Y.

B. I. D.

ULCER CONTROL

all day

all night 🥢

patient comfort

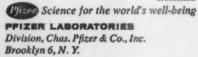
Natural Prolonged Action—The action of DARICON, a more potent and better tolerated anticholinergic, is consistently prolonged because it has a unique chemical structure and is not dependent on "mechanical" means (e.g., special coating, adsorption on ion-exchange resin).

In addition to peptic ulcer, DARICON, is also indicated for other gastrointestinal disorders characterized by hypersecretion, hypermotility and spasm (e.g., functional bowel syndrome, chronic nonspecific ulcerative colitis and biliary tract disease).

Dosage: 10 mg. b.i.d. (morning and evening). Supply: Tablets, 10 mg., white, scored. Bottles of 60 and 500.

*Trademark





POSITIVE EVIDENCE THAT "MEDIATRIC" INCREASES MUSCLE STRENGTH AND ENDURANCE

in less than five months, record of squeeze-bulb test shows repetition frequency increased from 31 to 50 consecutive times in left hand—much improved in right.*



*SQUEEZE-BULB MUSCLE ENDURANCE TEST Patient A.W., female, age 71

| "Mediatric" I first test and | herapy started at time of continued for 4½ months | Repetition (consecutiv | frequency e times) |
|---------------------------------|---|------------------------|-----------------------|
| | | Left hand | Right hand |
| 1st test | Feb. 16, 1954 | 31 | 58 |
| 2nd test | July 1, 1954 | 50 | 67 |



improved muscle endurance with steroid-nutritional therapy objectively demonstrated by physical tests

Muscle strength and endurance were determined by suff-bulb test in a

enhanced muscle endurance after continuous "Mediatric" therapy, even in short periods of eter, and joint range with a goniometer. These and other physical tests also showed

Mediatric" contains estrogen and androgen in amounts that will help counteract declining gonadal hormone secretion, maintain a positive nitrogen balance, and promote synthesis of

Combining both steroids and important nutritional supplements such as vitamin C, B12, other B vitamins and ferrous sulfate, "Mediatric" brings about increase in physical strength, overcomes general malaise, easy fatigability, lack of interest and vague pains in the bones and joints. In addition, "Mediatric" improves mental outlook and its general "tonic" effect is of especial benefit to your petient.

For better health and vigor in the older patient

"MEDIATRIC"

| STEROIDS TO THE STEEL ST | |
|--|--|
| Conjugated estrogens agains ("Premarin" 3 . 0.25 mg Methyliestosterone | |
| NUTRITIONAL SUPPLEMENTS | |
| Vicamin C. (ascorbie acid) | |

| | se (B1) | | |
|-------------------|---------|--|-----|
| | | | |
| | | | |
| | | | mg. |
| | | | Wg. |
| Folic acid U.S.P | | | |
| | | | |
| | | | |
| | | | |
| d-Desoxyephedrine | | | |

Suggested Dosages: Meto — I capsale or 1 teblat daily, or as required. Female — I capsule or 1 teblat daily, or as taken in 21 day courses with a rest period of one week between courses.

Supplied: Capsules — No. 252 — Bettles of 30, 100, and 1,000. Tabless — No. 752 — Bettles of 100 and 1,000.



THE AMERICAN COLLEGE OF PHYSICIANS Schedule of Postgraduate Courses, Spring, 1959

| | 77-76 | | | | | | |
|-------|---|---|--|---|---|---|---|
| June | 61-51 | | | | | * | |
| Ju | 21-8 | K: | tlantic Cit | eeting, A | M leunn | A .A.M. | V |
| | 1-5 | | | | * | | |
| | 52-56 | | | | | | |
| May | 18-22 | | | 23, | | | |
| M | 11-12 | | | | | | |
| | 8-1/ | | | | | 1 | |
| | 27-May 1 | | | | | | |
| | 70−24 | Si | cago, Illino | ion, Chi | sess Isun | .C.P. An | V |
| April | 13-12 | | 13, 14, 15 | | | | |
| Ψ. | 01-9 | | | | | | |
| | 7-4 | * | | | | | |
| | The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fees for all courses, other than Course No. 4, which will have a restricted registration, the fees will be: Members, \$60.00. For Course No. 4, which will have a restricted registration, the fees will be: Members, \$60.00: Non-members, \$80.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine St., Philadelphia 4, Pa. | Course No. 1, THE PRACTICE OF GLOBAL MEDICINE IN THE UNITED STATES: Cornell University Medical College, New York, N. Y.; Benjamin H. Kean, M.D., (Associate), Director. | Course No. 2, PRACTICAL REHABILITATION PROCEDURES FOR THE INTERNIST University of New York, Institute of Physical Medicine and Rehabilitation, Bellevue Medical Center, New York, N. Y.; Howard A. Rusk, M.D., F.A.C.P., Director; Edward W. Lowman, M.D., F.A.C.P., and Donald A. Covalt, M.D., Co-directors. | Course No. 3, CARDIAC ARRHYTHMIAS: Philadelphia General Hospital, Philadelphia, Pa.; Samuel Bellet, M.D., F.A.C.P., Director. | Course No. 4, PSYCHIATRY FOR THE INTERNIST: Psychiatric Institute, University of Maryland Hospital, Baltimore, Md.; Leo H. Bartemeier, M.D., F.A.C.P., and Ephraim T. Lisansky, M.D., F.A.C.P., Co-directors. | Course No. 5, SPECIAL TOPICS IN INTERNAL MEDICINE: University of Colorado Medical Center, Denver, Colo.; Gordon Meiklejohn, M.D., F.A.C.P., and C. Wesley Eisele, M.D., F.A.C.P., Co-directors. | Course No. 6, INTERNAL MEDICINE; SELECTED TOPICS: Cincinnati General Hospital, University of Cincinnati College of Medicine, Cincinnati, Ohio; Richard W. Vilter, M.D., F.A.C.P., Director, and John R. Braunstein, M.D., F.A.C.P., Associate Director. |

Amsterdam, Bernard: New York J. Med. 58:2199-2212 (July 1) 1958.

Panel Discussion on Proper Nutrition for the Older Age Group, J. Am. Geriatrics Soc. 6:787-802 (Nov.) 1958.

Leckert, J. T.; Donovan, C. B.; McHardy, G., and Cradic, H. E.: J. Louisiana M. Soc. 110:260-266 (Aug.) 1958.

blood cholesterol regulation is worth while . . .

Arcofac lowers blood cholesterol levels. The Arcofac regimen is safe...well tolerated... effective... and imposes no radical changes in diet.

Arcofac supplies linoleic acid, an essential polyunsaturated fatty acid that lowers high blood cholesterol levels. It also provides vitamin B₀ which is deemed necessary to convert linoleic acid into the primary essential fatty acid, arachidonic acid. Vitamin E, a powerful antioxidant, helps maintain the fatty acid in an unsaturated state.





Armour Cholesterol Lowering Factor

Each tablespoonful of Arcofac contains:

Essential fatty acids†...............6.8 Gm. (measured as linoleic) with 2.5 I. U. of Vitamin E*

Pyridoxine hydrochloride......1.0 mg. (Vitamin B₄)

†Supplied by safflower oil which contains the highest concentration of polyunsaturated fatty acids of any commercially available vegetable oil.

*Added as mixed Tocopherois Concentrate, N.F.



in management of the constipation "symptom-complex"

TWO NEW PRODUCTS

as convenient tablets . . . only 1 to 3 daily

for bulk

Celginace

Calcium and sodium alginates and dioctyl sodium sulfosuccinate, Mead Johnson

tablets granules

Celginace provides smooth, nonirritating, "hydrasorbent" bulk in the intestine, not in the stomach¹...

this avoids excessive gastric fulness and depression of appetite.

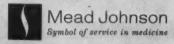
 Mulinos, M. G., and Glass, G. B. J.; Gastroenterology 24; 385-393 (May-Aug.) 1953.

for stool softening-bulk -peristaltic stimulation

tablets granules

When the patient presents a complex of symptoms and a comprehensive approach to therapy is indicated, Combinace provides (1) smooth, non-irritating, "hydrasorbent" bulk of alginates, (2) the predictable, yet gentle peristaltic stimulation of Peristim, ** (3) the moistening action of Colace.

A single product ... with three-fold effect.





the constipation "symptom-complex"

For each specific symptom or any combination of symptoms...you can select the anticonstipant which best meets the needs of the individual patient:

| | If the need is for | Colace®** | | |
|-------|---------------------------------|---------------|--|--|
| | softer, easier-to-pass stools | | | |
| - 486 | predictable, gentle peristaleis | Peri-Colaces† | | |
| N/E | bulk in the intestine | Celginace | | |
| | a combination of these effects | Combinace | | |

*Standardized preparation of anthraquimone derivatives from cascara agrada, Mead Johnson *Dioctyl sodium sulfosuccinate, Mead Johnson *Dioctyl sodium sulfosuccinate and anthraquinone derivatives from cascara, Mead Johnson

AN AMES CLINIQUICK

CLINICAL BRIEFS FROM MODERN PRACTICE

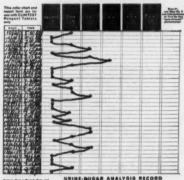
What differentiates "renal diabetes" (renal glycosuria) from diabetes mellitus?

Blood sugar levels. In renal glycosuria they are normal; in untreated diabetes, fasting blood sugars are usually 130 mg.% or over and postprandial levels 170 mg.%, or more.

Source: Joslin, E. P; Root, H. F; White, P, and Marble, A.: The Treatment of Diabetes Mellitus, ed. 9, Philadelphia, Lea & Febiger, 1952, pp. 701-702.

A "URINE-SUGAR PROFILE" FOR CLOSER CONTROL

The new CLINITEST Urine-Sugar Analysis Set contains an improved Analysis Record form that enables even closer control of the moderate and the severe diabetic. Daily urine-sugar readings may be connected to produce a graph—a day-to-day "profile" that reveals at a glance individual trends and degree of control.



URINE-PUGAR ANALYSIS RECORD

CLINITEST®



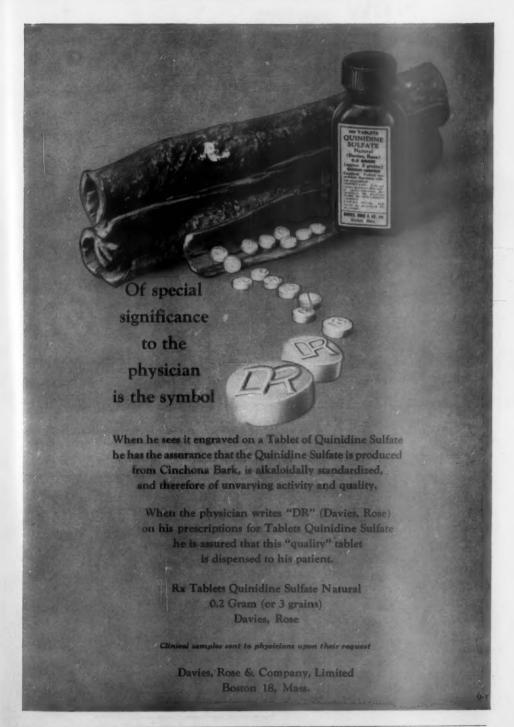
FOR EVEN BETTER CONTROL OF THE MODERATE AND THE SEVERE DIABETIC

the STANDARDIZED urine-sugar test for reliable quantitative estimations "... the most satisfactory method for home and office routine testing."*

*GP 16:121 (August) 1957.

AMES
COMPANY, INC
Elkhart - Indiana
Taronto - Canada



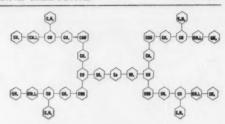


NEW

THERAPEUTIC CHEMICAL

IN

CONSTIPATION



Calcium Bis-(Dioctyl Sulfosuccinate)

The discovery by Wilson and Dickinson¹ at the University of Michigan that dioctyl sodium sulfosuccinate could correct constipation through fecal softening action marked a real advance in therapy. In cases of unimpaired bowel motility this new physico-chemical principle presented a new means of correcting bowel dysfunction without the need of catharsis.

Continuing research has now led to the development of a new therapeutic surfactant with more than double the surfactant effectiveness of the original dioctyl sodium sulfosuccinate.

This new substance, calcium bis-(dioctyl sulfosuccinate), reduces interfacial tension to a minimal value at a concentration of only 0.035 per cent. A minimal value of this order in dynes per centimeter requires 0.1 per cent or more of the older dioctyl sodium sulfosuccinate.

INTERFACIAL TENSION (Oil-Water Interface) Calcium Bis-(Dioctyl Sulfosticcin

| | (arcticin Bis-(Proctyl Surjosuccinate) | | |
|-----------|---|--|--|
| Dynes/cm. | Concentration | | |
| 55.0 | 0.00% | | |
| 13.3 | 0.01% | | |
| 9.9 | 0.02% | | |
| 8.4 | 0.03% | | |
| 7.4 | 0.035% | | |

Improved homogenization of the immiscible lipoid and aqueous phases of the intestinal content depends upon maximum reduction of interfacial tension. The greatest degree of fecal softening is achieved with surfactant agents capable of reducing interfacial tension to minimal values. Calcium bis-(dioctyl sulfosuccinate) represents a markedly more effective surfactant agent since maximum surfactancy results from less than half the concentration of previously used surfactants.

DOSAGE:

DOXICAL 240 mg. SOFT GELATIN CAPSULES—for adults, one daily.
DOXICAL 50 mg. SOFT GELATIN CAPSULES—for children and adults with minimum needs, one to three daily.

Wilson, J. L., and Dickinson,
 D. G.: J.A.M.A. 158:261-263
 (May 28) 1955.

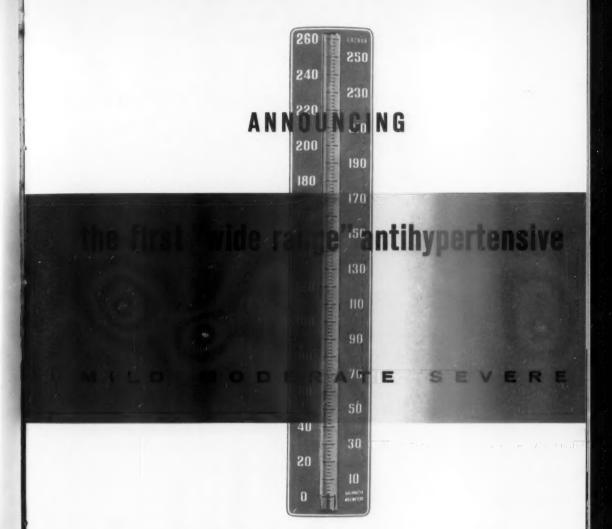
This new chemical, definitely superior in surfactant action, is indicated in the treatment of chronic constipation where non-laxative fecal softening therapy is the preferred regimen.

The usual adult dose is 240 mg. daily. For children and adults with minimum needs, 50 to 150 mg. daily may be given.

DOXICAL

LLOYD BROTHERS, INC.

CINCINNATI 3, OHIO



DIUPRES.

DIURIL, WITH RESERPINE

more hypertensives can be better controlled with DIUPRES than with any other agent ... with greater simplicity and convenience

a logical alliance of two antihypertensives you know and trust provides

increased effectiveness, decreased side effects

potentiated effect

DIUPRES produces an effect greater than either DIURIL or reserpine alone. It is effective in many patients who respond inadequately or not at all to either DIURIL or reserpine.

| 260 240 | 250 | Average anthrypertensive effect | | | Average antihypertensive effect of reserpine and DIURIL+reserpine in 7 patients? | | |
|------------|-------------|---------------------------------|---------------------------|---------------------------|--|----------------------|--------------------------------------|
| | 230 | after | 3 weeks | 12 weeks | control: | reserpine: | DIURIL |
| 220 | 210 | 6 months rauwolfia | after adding DIURIL | after adding DIURIL | | (12.3% reduction) | + reserpine: (26.2% reduction) |
| 200 | 210 | therapy | DIORIL | DIORIL | | | reduction) |
| | 190 | | | | | | |
| 180 | 170 | | | | - | | |
| 160 | | | _ | • | | | |
| 140 | 150 | | | | | | |
| 140 | 130 | | | | | | - |
| 120 | | | | | 100 | | |
| 100 | 110 | T A THE | | | | | |
| | 90 | | - 75- | 100 | | | |
| 80 | 70 | | | | | | |
| 60 | 1 " | | | | | | |
| | 50 | | | | | | |
| 40 | 30 | | | | | | |
| S0 | | -114 - | | - 111- | - 11 | - 10 | |
| | 10 | - 25 | 70 | | RU | | 100 |
| 0 | WILL METERS | | | | | | |

DIURIL WITH RESERPINE

effective therapy for most patients

DIUPRES by itself usually provides effective therapy for a majority of patients with mild or moderate hypertension, and even for many patients with severe hypertension. Many patients now treated with other agents which frequently cause distressing side effects can be adequately managed with well tolerated DIUPRES.

provides basic therapy

Should other drugs need to be added to DIUPRES, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.

rapid onset of effect

The antihypertensive action of DIUPRES is rapidly evident. (Considerable time may elapse before the antihypertensive effect of reserpine alone is observed.)

fewer and less severe side effects

DIUPRES may be expected to cause fewer and less severe side effects than are encountered with other antihypertensive therapy. (Since DIURIL and reserpine potentiate each other, the required dosage of each is usually less when given together as DIUPRES than when given alone. Such reduction in dosage makes side effects less likely to occur.)

often obviates weight gain

DIUPRES minimizes the problem of weight gain seen with reserpine (reserpine alone has been reported to produce weight gain in 50 per cent of patients).^{1,4}

virtually eliminates fluid retention

DIUPRES is not likely to cause either clinical or subclinical retention of sodium and water. (Hypotensive drugs, particularly rauwolfia⁵ and hydralazine,⁶ may cause fluid retention. Even when such retention is subclinical, their antihypertensive effectiveness is diminished.⁶)

diet more palatable

With DIUPRES, there is less need for rigid restriction of dietary salt, which patients find so burdensome.

> "It may well be that the drug [DIURIL] produces the benefits of a markedly restricted low sodium diet but without its hardships."3

subjective and objective improvement

DIUPRES allays anxiety and tension, thus reducing the emotional component of hypertension. Organic changes of hypertension may be arrested and reversed. Headache, dizziness, palpitations and tachycardia are usually promptly relieved by DIUPRES. When the *anginal syndrome* accompanies hypertension, the administration of DIUPRES may also cause diminution or even disappearance of this syndrome concurrent with control of the hypertension.

convenient, controlled dosage

Instead of two separate prescriptions, you write one prescription...the patient takes one tablet, rather than two different tablets...and the dosage schedule is easier for the patient to remember and follow.

"patients have fewer lapses and make fewer mistakes in dosage, the simpler the regimen can be made. Therefore I do not hesitate to use more than one medicament combined in one tablet, provided this gives approximately the correct dosage of each."6

economical

DIUPRES will cost the patient less than if he were given two separate prescriptions for its components.

Indications:

DIUPRES is indicated in hypertension of all degrees of severity. It can be used in the following ways:

- as total therapy
- as primary therapy, adding other drugs if necessary
- as replacement or adjunctive therapy in patients now treated with other agents

Precautions:

The precautions normally observed with DIURIL or reserpine apply to DIUPRES. Additional information on DIUPRES is available to physicians on request.

Recommended dosage range:

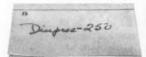
DIUPRES-500—one tablet one to three times a day.
DIUPRES-250—one tablet one to four times a day.

If necessary, other agents may be added. If the patient is receiving ganglion blocking agents or hydralazine, their dosage should be cut by 50 per cent when DIUPRES is added.



DIUPRES-500

500 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. Bottles of 100, 1000.



DIUPRES-250

250 mg. DIURIL (chlorothiazide), 0.125 mg. reserpine. Bottles of 100, 1000.

the first "wide range" antihypertensive

DUPRES

DIURIL, WITH RESERPINE

Rochelle, J. B., III, Bullock, A. C., and Ford, R. V.: Potentiation of antihypertensive therapy by use of chlorothiazide, J.A.M.A. 168:410, Sept. 27, 1958.
 Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E.: Treatment of essential hypertension with chlorothiazide (Diuril), J.A.M.A. 166:137, Jan. 11, 1958.
 Freis, E. D.: Treatment of hypertension. (Presented at the Annual Meeting of Southern Medical Association, Nov. 13, 1957.)
 Moyer, J. H., Dennis, E., and Ford, R.: Drug therapy (Rauwolfa) of hypertension, A.M.A. Arck. Int. Med. 96:530, Oct. 1955.
 Perera, G. A.: Edema and congestive failure related to administration of rauwolfa serpentina, J.A.M.A. 159:439, Oct. 1, 1955.
 Wilkins, R. W.: Precautions in use of antihypertensive drugs, including chlorothiaside, J.A.M.A. 167:301, June 14, 1958.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., Inc., PHILADELPHIA 1, PA.

*DIUPRES and DIURIL (chlorothiazide) are trademarks of Merck & Co., Inc.

what is the duration of
action
of the skeletal
muscle relaxant
you now
prescribe?

Chlorzoxazone

provides six hours' relief with a single oral dose.

specific for painful spasm

In arthritic, rheumatic, and traumatic muscle spasm. Paraflex relieves the stillness and pain effectively on an average dose of only 2 (ablets three or four times a day. Side effects are uncommon and seldom severe enough to require discontinuation of the drug.

Supplied: Liblets, scored, orange, bottles of 50. Each tablet contains Paraflex, 250 mg.

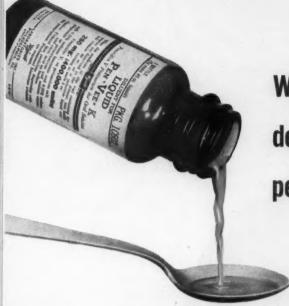
*Trade-mark

tll S Patent Pending

McNEIL

McNEIL LABORATORIUS INC · PHILADELPHIA 32, PA

19645



Wyeth brings you 2 delicious liquid forms of penicillin V potassium . . .

EIGUID



for Advertising



HIGH POTENCY (peach-flavored) 250 mg. (400,000 units) per 5-cc. teaspoonful; golden color

Supplied: Combination package of vial of dry powder and 1 bottle of diluent to make 40 cc.

MEDIUM POTENCY (raspberry-flavored) 125 mg. (200,000 units) per 5-cc. teaspoonful; raspberry color

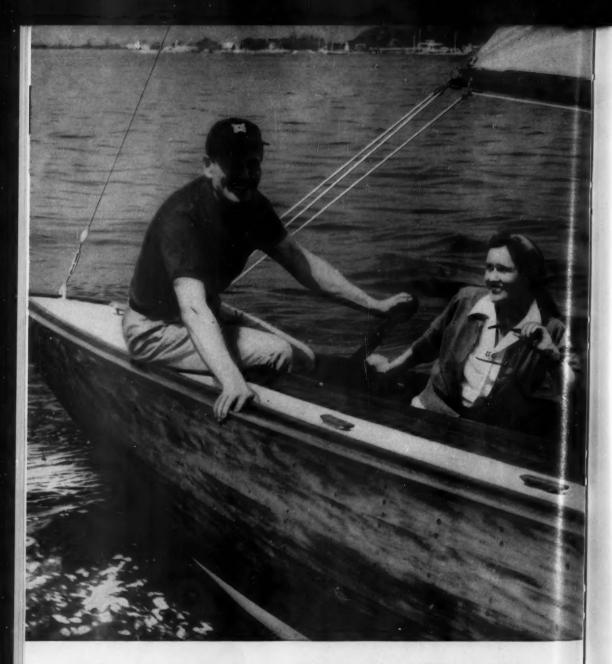
Supplied: Vial of powder to be reconstituted with water to make 40 cc.

blood levels in 15 minutes ... peak levels in 30 minutes



For taste-fussy patients of all ages, Liquid Pen•Vee K gives you two potencies and two fruit flavors for flexible, patient-accepted management. It is indicated for both prophylaxis and treatment in all infections responding to oral penicillin. Ready, reliable absorption and rapid, high blood levels assure clinically effective therapeutic action. Liquid Pen•Vee K is the only liquid preparation of penicillin V potassium in two strengths and two flavors.





Husbands, too, like "Premarin"

The physician who puts a woman on "Premarin" when she is suffering in the menopause usually makes her pleasant to live with once again. It is no easy thing for a man to take the stings and barbs of business life, then to come home to the turmoil of a woman "going through the change of life." If she is not on "Premarin," that is.

But have her begin estrogen replacement therapy with "Premarin" and it makes all the difference in the world. She experiences relief of physical distress and also that very real thing called a "sense of well-being" returns. She is a happy woman again — something for which husbands are grateful.

"Premarin," conjugated estrogens (equine), a complete natural estrogen complex, is available as tablets and liquid, and also in combination with meprobamate or methyltestosterone.

Ayerst Laboratories • New York 16, N. Y. Montreal, Canada



do you encounter SenearUsher isease?

then you should know...

Beneficial results with METICORTEN have been reported† in patients with Senear-Usher disease. Extensive documentation in the literature demonstrates the unsurpassed therapeutic effectiveness of this established steroid in all corticosteroid-responsive disorders.

METICORTEN® (prednisone) is available as 1, 2.5 and 5 mg. white tablets.

*Senear-Usher disease—also called pemphigus erythematosus—is a dermatosis resembling pemphigus vulgaris involving mainly the head, face, and trunk. Whether common or rare, response to METICORTEN is excellent in most allergic and inflammatory skin diseases.

†Henington, V. M.; Kennedy, B., and Loria, P. R.: South. M. J. 51:577, 1958.

Schering EW JERSEY

SCHERING CORPORATION · BLOOMFIELD, NEW JERSEY

quimico (Meti study), Janeiro, Nove (16) Blanchi, rheumatoid at gust 14-19, 195 erman, H. A. R. L.: Bollet. Atlantic City erythematosus Assoc., Atlanti and Tedeschi, and Ficini, M. ences with met Rheumat., Rio Comparative st Meticort Acad. Med. Costa, P. (36) Acad. York Preliminary properties Assoc., Bethes Bollet, A. J.: and Bollet, A and Bauer, W. and Bauer, nitrogen, and of June 3-4, 193 (42) Carrizosa posium, Nation C. A.; Orcese, (44) Cecil, R. Philadelphia, Wallace, E. Z. secretion in the June 1, 1955. arthritis, Fin Firs (47) Cohen, with metacorta New York, Ma others: Rev. (49) Craver, metacortandraci May 31 and Ju experiences wi June 1, 1955. Ragan, C.: J 8:545, 1955. at New York . E. J.: Studies Internat. Conf. and Gluck, E. and Baquiche, and comments: (62) Occid. 1955. (64) Fer metacortand Meticorten, Ne Mosca, M. C., V.; Ginoulhia (July 4) 1955. and Carbone, measured by p secretion in ma (68) Freisleder R. H.: Experidralone for in-York, May 31 (July 4) 1955. the treatment Rheumat., Ric Meticorten in York, May 3 Zabaleta. (Clinical

Studies



DEXAMYL* SPANSULE

capsules make it easier for your overweight patient to maintain a low-calorie diet because they

- · afford relief from the tension and anxiety which so frequently accompany caloric restriction
- · provide positive daylong control of appetite both at and between meals

When the overweight patient is particularly listless and lethargic-

DEXEDRINE: SPANSULE capsules provide daylong control of appetite as well as gentle stimulation.

tablets · elixir · 'Spansule' capsules

SMITH KLINE & FRENCH LABORATORIES, PHILADELPHIA



*T.M. Reg. U.S. Pat. Off. for 'Dexedrine' plus amobarbital †T.M. Reg. U.S. Pat. Off. for sustained release capsules,

T.M. Reg. U.S. Pat. Off. for dextro-amphetamine sulfate,

SMOTHERED WITH AIR

IN CHRONIC BRONCHITIS AND ASTHMA, Choledyl helps improve pulmonary function in the patient with emphysematous changes by letting air out as well as in. As aeration of the lungs is enhanced, breathing is eased, coughing and wheezing are reduced, and acute episodes of bronchospasm are often eliminated. Choledyl, the choline salt of theophylline, produces therapeutic blood levels orally without the gastric distress that accompanies aminophylline. Average adult dosage is one 200 mg. tablet q.i.d. Maximum results are usually achieved within two weeks.



CHOLEDYL

betters breathing...forestalls the crisis

NOW even many cardiac patients may have THE FULL BENEFITS OF CORTICOSTEROID THERAPY

DECADRON—the new and most potent of all corticosteroids, eliminated fluid retention in all but 0.3 percent of 1500 patients†, and induced beneficial diuresis in nearly all cases of pre-existing edema.



treats <u>more</u> patients more effectively Therapy with DECADRON has also been distinguished by virtual absence of diabetogenic effects and hypertension, by fewer and milder Cushingoid reactions, and by freedom from any new or "peculiar" side effects. Moreover, DECADRON has helped restore a "natural" sense of well-being.

†Analysis of clinical reports.

*DECADRON is a trademark of Merck & Co., Inc., ©1958 Merck & Co., Inc.



MERCK SHARP & DOHME

Division of Merck & Co., Inc., Philadelphia 1, Pa.



"RAUTRAX IS A SQUISS TRADEMAR

Unsurpassed symptomatic relief testifies to Medrol's enhanced anti-inflammatory, anti-allergic effects. But in corticotherapy that is not enough. The key to the patient's total welfare is the therapeutic ratio-

DESIRED EFFECTS

Therapeutic

Ratio

TO UNDESIRED EFFECTS

Here is where Medrol stands out. For all its increased effectiveness, Medrol has fewer and milder "classic" corticoid side effects; no disturbing "new" side effects such as muscle weakness. Whenever corticotherapy is indicated, remember that Medrol has the best therapeutic ratio in the steroid field.



The best therapeutic < in the steroid field makes

Medrol

the choice of physicians who consider the total welfare of their patients

*Trademark, Reg. U. S. Pat. Off .- methylprednisolone, Upjohn

Upfohm The Upjohn Company, Kalamazoo, Michigan

Keep
the "reducer"
happy

HEDRINE"
in OBESITY

means help

- For those who eat too much
- For those who are depressed

'Methedrine' dispels abnormal craving for food, subtly elevates the mood.

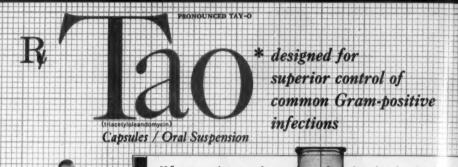
'Methedrine's brand Methamphetamine Hydrochloride Tablets 5 mg., scored



BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

Please Mention this Journal when writing to Advertisers

ag





in the patient:

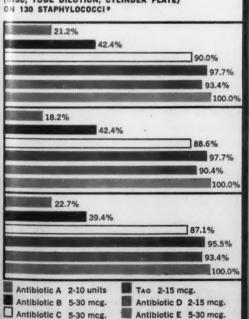
95% effective in published cases1-0

| Conditions treated | No. of Patients | euros (| Improved | Failure |
|---|--|---------|---------------|---------|
| ALL INFECTIONS | 558 | 448 | 80 | 30 |
| Respiratory Infections | 258 | 208 | 31 | 390318 |
| Pharyngitis and/or tonsillitis | 65 | 58 | 5 | 2 |
| Pneumonia | 90 | 68 | 17 | 7 |
| Infectious asthma Otitis media | 31 | 38 13 | | -6 |
| Other respiratory | 28 | 372 | | |
| (bronchitis, bronchiolitis, bronchiectasis, pneumonitis, laryngotracheitis, strep throat) | 20 | | | |
| Skin and soft tissue infections | 230 | 191 | 38 | |
| Infected wounds, incisions and lacerations | 41 | | | |
| Abscesses | 51 | 1 | | 3000 |
| Furunculosis | -58 | | | |
| Acne, pustular | 43 | | 15 | |
| Pyoderma | 19 | | | |
| Other skin and soft tissue (infected burns, cellulitis, impetigo, uicers, others) | 18 | | 1 | |
| Genitourinary infections | 28 | 39 | SET MAN | 1208 |
| Acute pyelitis and cystitis | 10 | | 2 | |
| Urethritis with gonorrhea or cystitis | 8 | | | |
| Pyeionephritis | 4 | | | 3 4 |
| Salpingitis Pelvic inflammation with endometriosis | 5 | | A 4 . 1000 | 3 |
| Pelvic Inflammation with endometriosis | . 1 | | | |
| Miscellaneous | 42 | | | 1. 4 |
| (adenitis, enteritis, enterocolitis, subacute bacterial endocarditis, fever. | | | N. 4 8 5 15 1 | |
| hematoma, staphylococcus carriers, | | | | |
| osteomyelitis, tenosynovitis, septic | | | | |
| arthritis, acute bursitis, periarthritis) | - | | 是一個學出 | |
| | A CONTRACTOR OF THE PARTY OF TH | | | |

in the aboratory:

over 90% effective against resistant staph

COMPARATIVE TESTS BY THREE METHODS
(DISC, TUBE DILUTION, CYLINDER PLATE)



Percentage of organisms inhibited by the range of concentrations listed for each antibiotic.

Other Tao advantages:

Rapidly absorbed - stable in gastric acid, TAO needs no retarding protective coating

Low in toxicity – freedom from side effects in 96% of patients treated; cessation of therapy is rarely required

Highly palatable — "practically tasteless"? active ingredient in a pleasant cherry-flavored medium.

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children 8 months to 8 years, a daily dose of approximately 30 mg./Kg. body weight in divided doses has been found effective. Since TAO is therapeutically stable in gastric acid, it may be administered without regard to meals.

Supplied: TAO Capsules—250 mg, and 125 mg, bottles of 60. TAO for Oral Suspension—1.5 Gm., 125 mg, per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. Koch, R., and Asay, L. D.: J. Pediat, in press. 2. Leming, B. H., Jr., et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 3. Mellman, et al.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 4. Olansky, S., and McCormick, G. E., Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 5. Shubin, H., et al.: Antibiotics Annual 1957-1958, New York, N. Y., Medical Encyclopedia, Inc., 1958, p. 679. 6. Isenberg, H., and Karelitz, S.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 7. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy 5:527 (Aug.) 1958. 8. Kaplan, M. A., and Goldin, M.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958. 9. Truant, J. P.: Paper presented at the Symposium on Antibiotics, Washington, D. C., Oct. 15-17, 1958.

Tao dosage forms— for specific clinical situations

Tao Pediatric Drops

For children-flavorful, easy to administer.

Supplied: When reconstituted, 100 mg. per cc. Special calibrated droppers—5 drops (approx. 25 mg.) and 10 drops (approx. 50 mg.).

TAC-AC (TAO analgesic, entihistaminic compound)

To eradicate pain and physical discomfort in respiratory disorders.

Supplied: In bottles of 36 capsules.

TAOMID* (Tao with triple sulfas)

For dual control of Gram-positive and Gram-negative infections.

Supplied: Tablets, bottles of 60. Oral Suspension, bottles of 60 cc.

Intramuscular or intravenous

For direct action—in clinical emergencies. Supplied: In 10 cc. vials.

......



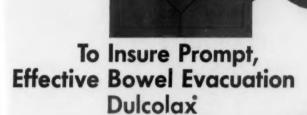
New York 17, N.Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being

INDEX TO ADVERTISERS

MARCH, 1959

| Abbott Laboratories |
|--|
| A.C.P. Postgraduate Courses |
| Ames Company, Inc |
| A.I.M. Wanted Back Issues 5, 116 |
| Armour Pharmaceutical Company |
| Astra Pharmaceutical Products. Inc. 96, 110 |
| Ayerst Laboratories 12-13, 28-29, 64, 130-131, 142 |
| Burdlek Corporation, The 120 |
| Burroughs Wellcome & Co. (U.S.A.) Inc. 62, 149 |
| Burton, Parsons & Company 91 |
| Central Soya Company, Inc. 74 |
| Ciba Pharmaceutical Products, Inc |
| Warren E. Collins, Inc. 5 |
| Cutter Laboratories |
| Davies Rose & Company, Limited |
| Eaton Laboratories |
| Endo Products, Inc |
| E. Fougera & Co. Inc |
| Geigy Chemical Corporation |
| General Electric Company |
| Paul B. Hoeber, Inc |
| Hyland Laboratories 97 |
| Irwin Neisler & Company |
| Lea & Febiger |
| Lederle Laboratories, Div. American Cyanamid Co |
| Thos. Leeming & Company |
| Eli Lilly & Company Third Cover |
| Lloyd Brothers, Inc |
| Macmillan Company, The |
| McNeil Laboratories, Inc. 139 Mead Johnson & Company 25, 134–135 |
| Merck, Sharp & Dohme Insert Facing Page 138, 8-9, 38, 54, 61, 78, 88-87, 114, 123, 146 |
| Wm. S. Merrell Company, The |
| Ortho Pharmaceutical Corp |
| Pfizer Laboratories, Div. Chas. Pfizer Co., Inc |
| Pitman-Moore Company 78 |
| Riker Laboratories, Inc. Second Cover, 4, 102 |
| Bitter Company, Inc. 117 |
| A. H. Robins Company 82, 119 |
| Roche Laboratories, Div. Hoffmann-La Roche, Inc. 15, 75, 92-93 |
| J. B. Roerig & Company |
| Wm. H. Rorer, Inc |
| Sanborn Company |
| W. B. Saunders Company 6 |
| Schering Corporation |
| Schieffelin & Co |
| G. D. Searle & Co |
| Sherman Laboratories |
| Smith, Kline & French Laboratories |
| E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. |
| 11, 17, 30, 44, 55, 67, 80, 99, 112-113, 118, 126-127, 147 R. J. Strasenburg Co |
| |
| United Air Lines |
| Upjohn Company, The 148 U. S. Vitamin Corporation 104-105 |
| D. Van Nostrand Company, Inc. 5 |
| Virginia Hot Springs |
| Waliace Laboratories |
| Warner-Chilcott Laboratories |
| Warren-Toed Products, Inc |
| White Laboratories, Inc |
| Winthrop Laboratories, Inc |
| Woodward Medical Personnel Bureau |
| Wyeth Laboratories Insert Facing Page 16, 24, 31, 40, 46-47, 52, 63, 88, 98, 121, 125, 140-141 |
| |





Dulcolax — in either tablet or suppository form — insures

by systemic

cts on the large bo

Is equally effective whether ministered orally or by suppository.

Dosage: Tablets—1 to 3 (usually 2) at bedtime for bowel movement the following morning, or ½ hour before breakfast for a movement within six hours. Tablets are enteric coated, and must be taken whole, not chewed or crushed; they should not be taken with antacids. Suppositories—1 at the time a bowel movement is required.

Supplied: Dulcolax® (brand of bisacody!). Yellow enteric-coated tablets of 5 mg. in boxes of 6 and bottles of 100. Suppositories of 10 mg. in boxes of 6. Under license from C. H. Boehringer Sohn, Ingelheim.

Contact Laxative

Geigy



TACHYCARDIA -ALMOST WITHOUT REGARD TO CAUSE— CAN NOW BE CONSIDERED AN INDICATION FOR SERPASIL®

(reserpine CIBA

The heart-slowing action of Serpasil can be of therapeutic value in a wide variety of conditions marked by an increased heart rate. • Serpasil prolongs diastole, allowing more time for the myocardium to recover and enhancing cardiac blood flow and efficiency.¹ This heart-slowing effect is unrelated to the antihypertensive effect of Serpasil; that is, in normotensive patients with tachycardia, Serpasil will slow heart rate without decreasing blood pressure. • Serpasil is thought to slow the heart by central suppression of afferent sympathetic activity,² thus inhibiting impulses to the cardio-accelerator fibers and allowing the normal braking action of the vagus to predominate. This heart-slowing action is unlike that of the agents now in widespread use—the veratrum derivatives, digitalis, quinidine, and parasympathomimetic agents. Serpasil is virtually free of the dangers (heart block, cardiac arrest) and the disadvantages of "titrating" dosage heretofore encountered with bradycrotic drugs.

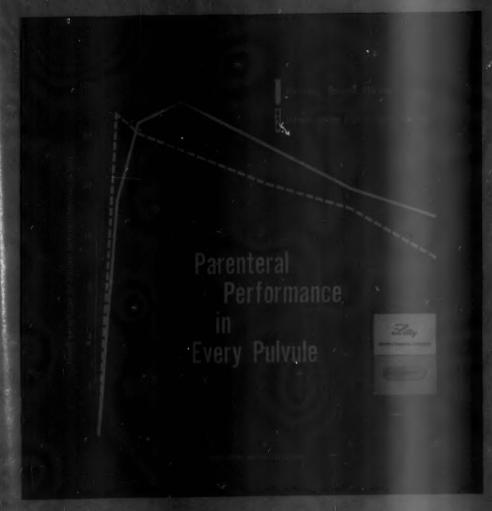
SERPASIL HAS PROVED EFFECTIVE AS A HEART-SLOWING AGENT IN THE FOLLOWING CONDITIONS:

MITRAL DISEASE³⁻⁵ • MYOCARDIAL INFARCTION⁵ • CARDIAC ARRHYTHMIAS⁶⁻¹¹ • NEUROCIRCULATORY ASTHENIA^{6,10,12} • THYROID TOXICOSIS^{5,10,13} • EXCITEMENT AND EFFORT SYNDROMES⁶ • CARDIAC NEUROSIS^{6,10,13} • CONGESTIVE FAILURE^{8,11,14,15}

NOTE: In patients receiving digitalis or quinidine, Serpasil therapy should be initiated with especially careful observation. Serpasil is not recommended in cases of aortic insufficiency.

DOSAGE FOR TACHYCARDIA: Dose range is 0.1 to 0.5 mg. per day. Rapid heart rate usually will be relieved within 1 to 2 weeks, at which time the daily dose should be reduced. SUPPLIED: Tablets, 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg. Elizirs, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon. Samples available on request. References: 1. Cotten, H. B., Herren, W. S., McAdory, W. C., and Klapper, M. S.: Am. J. M. Sc. 230:408 (Oct.) 1955. 2. Schneider, J. A.: Am. J. Physiol. 181:64 (April) 1955. 3. Schumann, H.: Ztschr. Kreislaufforsch. 43:614 (May) 1954. 4. Schumann, H.: Klin. Wchnschr. 33:124 (Feb.) 1955. 5. Schumann, H.: Ztschr. Kreislaufforsch. 45:115 (Feb.) 1956. 6. Halprin, H.: J. M. Soc. New Jersey 52:616 (Dec.) 1955. 7. Hollister, L. E.: Personal communication 1956. 8. Achor, R. W. P., Hanson, N. O., and Gifford, R. W., Jr.: J.A.M.A. 159:841 (Oct. 29) 1955. 9. Harris, R.: Ann. New York Acad. Sc. 59:95 (April 30) 1954. 10. Schumann, H.: Ztschr. Kreislaufforsch. 43:614 (May) 1954. 11. Hughes, W., Dennis, E., McConn, R., Ford, R., and Moyer, J. H.: Am. J. M. Sc. 228:21 (July) 1954. 22. Wiggers, C. J.: Physiology in Health and Disease, 5th Ed., Lea & Febiger, Philadelphia, 1949, p. 328. 13. Zaky, H. A.: Lancet 2:600 (Sept. 18) 1954. 14. Perera, G. A.: J.A.M.A. 159:439 (Oct. 1) 1955. 15. Avol, M., and Vogel, P. J.: J.A.M.A. 159:1516 (Dec. 17) 1955.

s/sees....



iLOSONE assures a decisive response in common bacterial infections

Parenteral potency. The graph above shows that floograp provides anti-bacterial serum levels comparable to those obtaining the first administration.

Parenteral certainty—in more than a thousand determineticle, in hundreds of patients studied, liosees has never failed to provide alguificant antibecterial levels in the serum.

The usual dosage for adults and chil-

dren over fifty pounds is 250 mg, every six hours, but doses of 500 mg, or more may be administered safely every six hours in more severe infections. For optimum enect, administer on an empty stomach. Supplied in Pulvales of 250 mg, (For children under fifty pounds, a 125-mg, Pulvule is also available.)

1. Antibiotic Med. & Clin. Therapy, 2005, 1992.
2. Data from Antibiotics Annual, p. 200, 1984, 1986.

m complete a discommente activi & Chi.

BLI LILLY AND COMPANY F INDIANAPOLIC C. INDIANA, U. B. A.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PERIODICANS

EDITOR
MAUDICE C. PINCOPTS, M.D., Baltimore

ASSOCIATE EDITOR

FRED R. MCCRUMB, M.D., Baltimore

EDITORIAL BOARD

CHESTER M. JONES, M.D., Boston, Chairman

ALEX. M. BURGESS, SR., M.D., Providence THOMAS FINDLEY, M.D., Augusta

A. CARLTON ERNSTENE, M.D., Cleveland RICHARD A. KERN, M.D., Philadelphia

IRVING S. WRIGHT, M.D., New York

EDWARD R. LOVETA VD. Philadelphia

Editorial Office—University Hospital, Bultimore 1, Maryland Executive Office—4200 Pine Street, Philadelphia 4, Pa. Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review, should be addressed to the Editor. Bibliographic references are to conform to the following state:

A Doe I E What I know short it, I A M A 98, 2006 1031

Six illustrations per article are allowed without cost to the author. Beyond this author the author must pay the actual cost of illustrations.

REPERNIS. For each article published, there will be furnished grans hity reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

Reviews. Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material viewed monthly in the ANNALS. Since it is not possible to review all books submitted, a monthly should send it to the Editor. Since it is not possible to review all books submitted, a monthly should send in the review section.

Subscription. This periodical is issued monthly, new volunces beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: \$10.00, ary and July numbers of each year. Subscription price per annum, net postpaid: \$10.00, united States, Canada, Hawaii, and Puerto Rico; \$7.00, in the above countries, to be paid to medical students, interns and residents; \$12.00, other countries. Prices for back itembers furnished upon application. Single numbers, current volume, when available, \$1.25, the countries of the price of the countries of the price of the countries. Treatment, and remitted the countries of the countr

BUSINESS CORRESPONDENCE. All correspondence to ating to Business meets, advertising subscriptions to the Annacs, inquiries concerning membership to the Annacs of t

